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Clinical Potassium Problems

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SUMMARY

Alterations in serum potassium are common in many diseases. In a series of 390 determinations of serum potassium, the levels found were low in 24 per cent and high in 2.6 per cent.

The major causes of low serum potassium are (1) decreased potassium intake due to intravenous feedings which do not contain potassium; (2) increased loss of potassium in the urine due to accelerated tissue breakdown, or renal lesions; (3) loss from the gastrointestinal tract due to diarrhea, or fistulae, and (4) shift between serum and cells, due to metabolic causes, drugs or changes in pH.

The major cause of high serum potassium is uremia with renal retention.

Clinical symptoms and signs of low body potassium include muscle weakness and paralysis, which may lead to death in respiratory failure if not corrected, tachycardia, gallop rhythm, dilatation of the heart. The electrocardiogram shows inverted, low amplitude, or isoelectric T waves and a prolonged QT interval.

Potassium chloride orally, subcutaneously or intravenously is recommended for use in the treatment of potassium deficits. It should not be used in the presence of oliguria or anuria or dehydration. The amounts of potassium necessary to correct deficits vary widely and cannot be predicted from the serum level. Special reference is made to the prevention and therapy of potassium deficits in diabetic acidosis.

High serum potassium levels are difficult to correct. Suggested measures are administration of glucose, insulin or calcium, gastric or peritoneal lavage or use of the artificial kidney.

UNTIL recently serum potassium levels have been determined in only a few diseases, and usually only by research laboratories, due to the time and difficulty involved in the chemical determination. A rapid yet accurate method is now available to the clinical laboratory with the development and improvement of the flame photometer.[3, 26]

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INCIDENCE OF ABNORMAL POTASSIUM LEVELS

The widespread alterations in serum potassium which may occur clinically are becoming increasingly apparent as more tests are made. This is illustrated in Table 1 which shows the incidence and the abnormal values found during one month in a large county hospital. It is significant that 27 per cent of the 390 determinations made were abnormal, with 24 per cent low and 2.6 per cent high. With one exception, the high serum potassium values were found in patients with uremia, and were due to

renal retention of potassium. The low serum potassium values were found in a wide variety of conditions. On the surgical service the vast majority were due to inadequate intake of potassium in the postoperative state, because of prolonged use of parenteral fluids without potassium, combined with nasogastric suction, and alkalosis. A few cases were associated with intestinal fistulae and increased loss of potassium by this route. On the medical service the conditions associated with low serum potassium levels included poor intake of food due to wasting diseases, prolonged use of intravenous feedings without potassium, diabetic acidosis under treatment, Addison's disease treated with desoxycorticosterone acetate, and acute pancreatitis.[14]

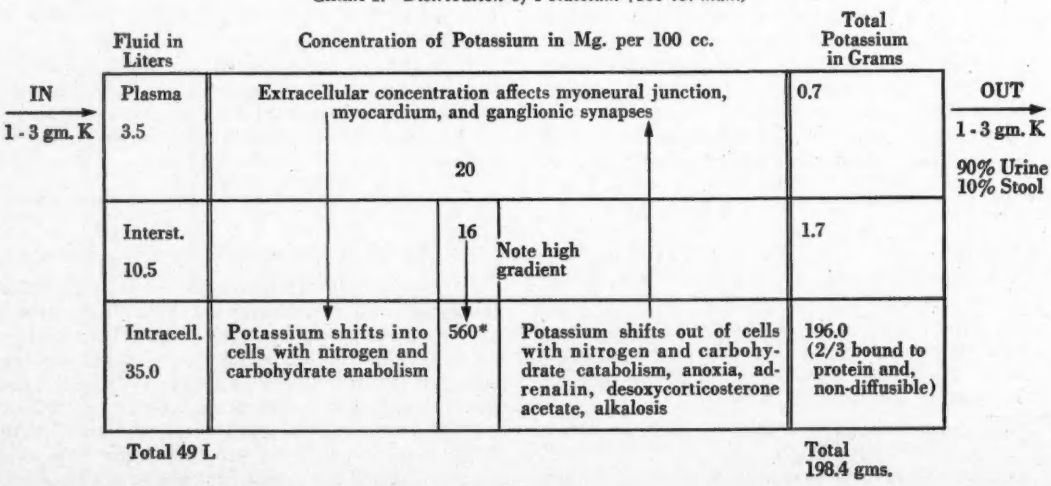
NORMAL POTASSIUM BALANCE

To understand the alterations in potassium which occur in disease, it is necessary to consider the normal movements and distribution of potassium in the body. This can be schematically represented (Chart 1). In the average diet there are 1 to 3 gm. of potassium (meat, nuts, vegetables, fruit, milk). The urinary output of potassium about equals the intake, if cellular levels and renal function are normal. There is a constant turn-over of potassium in the body, as demonstrated by studies with radioactive potassium,[18] but the total balance remains constant if the intake and output are equal. Potassium is present in very low concentrations (16 to 20 mg. per 100 cc.) in the plasma and interstitial fluid. The extracellular concentration, although low, appears to be necessary for the activation of acetylcholine and transmission of the electrical impulse along nerves or across the myoneural junction.[17] The exact role of potassium, however, in neuromuscular physiology is largely unsettled. The great bulk of the body potassium is in the cells, where it is the major cation. This is in contrast to the position of sodium, which under usual conditions is the major extracellular cation, with low intracellular concentrations. Two-thirds of the cellular potassium is bound to protein and does not diffuse. The remainder passes in and out of the cell. The mechanism of the passage of potassium through the cell membrane is poorly understood, and may be under chemical, physical or hormonal control. It is to be noted that potassium enters the cell against a very high diffusion gradient. It is known that potassium shifts into the cells during protein[1, 31] or carbohydrate[16] anabolism, and out of the cells during tissue breakdown and in alkalosis.[11, 12] Adrenalin,[13] desoxycorticosterone acetate,[19, 46] and digitalis[7] may also cause a shift of potassium out of the cells. Potassium administration causes the disappearance of ectopic heart beats resulting from toxic levels of the digitalis glycosides.[41]

TABLE 1.—*390 Serum Potassium Determinations, Los Angeles County General Hospital*

I. *Number of Low Serum Potassium Levels* (under 14 mg. per 100 cc.)	92 (24%)
A. *Surgical Service* — Gastrointestinal suction, intravenous feedings, fistulae.	55
B. *Medical Service* — Malnutrition, intravenous feedings, diarrhea, treatment of diabetic acidosis, treatment of Addison's disease, acute pancreatitis, thyroid crisis.	37
II. *Number of High Serum Potassium Levels* (over 25 mg. per 100 cc.)	10 (2.6%)
All but one due to renal failure.	

CHART 1.—*Distribution of Potassium (150 lb. man.)*



*This is the figure given by Gamble,[23] and in view of recent biopsy studies may be too high.

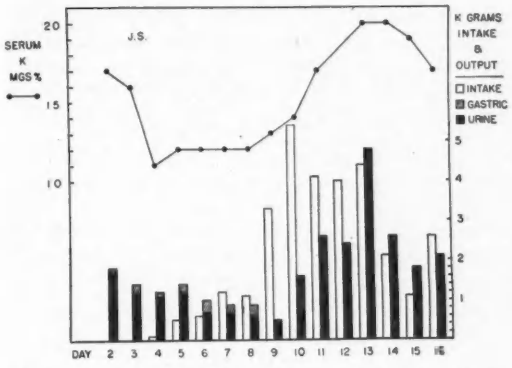


Chart 2.—Potassium balance in postoperative patient (white male, aged 13).

MECHANISMS OF CHANGES IN POTASSIUM IN DISEASE

The three mechanisms which can cause shifts in serum potassium levels are: Changes in intake, changes in output, and shifts between cells and serum.

Low Serum Potassium:

Inadequate intake of potassium is the most frequent clinical cause of low serum and cellular potassium levels. As the urine apparently never is potassium-free, continued urinary excretion of potassium explains the fall in body potassium when there is no intake. This is illustrated in Chart 2. The patient in the case from which the chart was drawn, a young boy with a ruptured appendix and generalized peritonitis, had vomited and had had diarrhea for several days before entry. In four days without intake of potassium, the serum level fell from 17 to 11 mg. per 100 cc. Intake of 0.6 to 1.2 gm. of potassium a day maintained the serum level at 12 mg. per 100 cc. from day 5 to day 9. The patient received 3 to 5 gm. daily for five days (days 9 to 14) before correction of the serum potassium deficit occurred. It is to be noted that potassium continued to be lost in the urine in amounts of 1.1 to 1.7 gm. per day during the period when there was no potassium intake. Urinary output of potassium increased as the body deficit was corrected, and the intake increased. The loss of potassium by nasogastric suction (0.1 to 0.3 gm. daily) contributed slightly to the potassium deficit.

Increased excretion of potassium in the urine is related to increased nitrogen excretion due to any cause (increased tissue breakdown due to infection, neoplasm, uncontrolled diabetes,[2] starvation, following trauma, and postoperative states.[1, 31]) Here potassium shifts out of the cells with nitrogen. Certain drugs, such as desoxycorticosterone acetate[19] and large saline infusions[44] cause an increased loss of potassium in the urine, also. Certain patients with chronic renal disease excrete large amounts of potassium in the urine.[4]

The problem of the renal control of potassium is still unsolved. In general, patients continue to excrete potassium (as illustrated in Chart 2), even though there is a body deficit of potassium.[45] However, the authors have observed a few patients with serious potassium deficits who have conserved potassium as vigorously as sodium, excreting urine exceedingly low in potassium—8 to 10 mg. per 100 cc. The normal individual tends to excrete extra potassium which is ingested.[45] If there is a body deficit of potassium, ingested potassium is largely retained.[45] The elevated serum potassium levels occurring in uremia are due to decreased glomerular filtration.[15] At high and normal serum potassium levels the kidney both filters and secretes potassium.[38]

While normally only a small part of potassium (10 per cent) is excreted in the stool, in the presence of diarrhea or fistulae sizeable losses may occur.[33] This was first emphasized by Darrow[10] in infantile diarrhea, but it has now been shown to occur in other types of diarrhea, as sprue.[27] Small amounts of potassium are present in the gastric juice, and are lost to the body by use of nasogastric suction or prolonged vomiting. This loss may be accentuated by using distilled water for irrigation of the suction apparatus.

The shift from serum to cells occurs during nitrogen and carbohydrate anabolism. The intensive insulin therapy of diabetic acidosis causes serum potassium to fall,[28, 30, 34] presumably due to a movement of potassium into the cell with carbohydrate.[16] Intensive glucose treatment in the non-diabetic may also cause a shift of potassium into the cell.[21] In familial periodic paralysis there occurs a spontaneous shift from the serum to the cells.[24] As this frequently follows carbohydrate ingestion, it is suggested that increased uptake of potassium by the cells in carbohydrate anabolism is responsible. Testosterone causes a shift of potassium into the cells during protein anabolism.[5] Potassium moves out of the cell in both acidosis[2] and alkalosis.[11, 12] A cellular and serum deficit of potassium occurs in all types of metabolic alkalosis and its correction is essential in the treatment of the alkalosis.

High Serum Potassium:

Decreased glomerular filtration[15] occurring in both acute and chronic renal disease and associated with nitrogen retention and excessively high intakes of potassium is the major cause of high serum potassium levels. The serum level is also raised in dehydration.

DISEASE STATES ASSOCIATED WITH POTASSIUM CHANGES

A summary of the disease states associated with potassium disorders, with the mechanism of the change in potassium values, is shown in Table 2.

Alterations in Muscle Potassium Content:

In general, low serum potassium levels are associated with decreased potassium concentrations in

the cell. There are a few exceptions. In familial periodic paralysis the muscle levels of potassium are normal with a low serum level. This also occurs following the use of testosterone. In the severe dehydration in untreated diabetic acidosis the muscle levels of potassium may be low with elevated serum levels. This may also occur during intravenous therapy of low serum potassium levels due to any cause. Low muscle levels of potassium are found in myotonia congenita and nutritional muscular dystrophies.[8] In myasthenia gravis the muscle level may be high,[18] but this is rare, as it is difficult to greatly increase the muscle potassium content. High serum potassium levels may be associated with slightly elevated, normal or low muscle potassium content.

THE EFFECTS OF CHANGES IN BODY POTASSIUM

As many abnormal serum potassium values are being found (Table 1), it becomes important clinically to evaluate the effects of changes in body potassium in order to decide when treatment is indicated. A summary of the effects of potassium

TABLE 2.—*Disease States Associated with Abnormal Potassium Levels*

Low Serum Potassium:

Clinical Condition	*Mechanism of Shift in Potassium*
1. Any illness, particularly postoperative states, with prolonged use of intravenous feedings not containing potassium.	1. Inadequate intake of potassium.
2. Chronic wasting diseases, with malnutrition, as malignancy, advanced congestive heart failure, tuberculosis or starvation.	2. Inadequate intake of potassium.
3. Conditions which may be associated with negative nitrogen balance: a. Postoperative states. b. Trauma, as crushing injuries. c. Infections. d. Uncontrolled diabetes. e. Acute anoxia.	3. Increased loss of potassium with nitrogen in the urine.
4. Loss of gastrointestinal content. a. Diarrhea—all types. b. Gastrointestinal fistula—pancreatic, biliary and fecal.	4. Loss of potassium in gastrointestinal content, plus poor absorption.
5. Familial periodic paralysis.	5. Shift from serum to cells.
6. Diabetic acidosis during therapy.	6. Increased loss in urine before therapy. Shift from cells to serum with insulin therapy.
7. Addison's disease, treated with desoxycorticosterone acetate.	7. Shift from cells to serum with increased loss in urine.
8. Metabolic alkalosis.	8. Increased loss in urine.
9. Cushing's disease with alkalosis.	9. Increased loss in urine.
10. Chronic renal disease (rare patient with more tubular than glomerular involvement).	10. Increased loss in urine.
11. Lower nephron nephrosis (recovery stage with diuresis).	11. Increased loss in urine.
12. Hyperthyroidism (rare).	12. Shift from serum into cells.
13. Acute pancreatitis.	13. Uncertain.

High Serum Potassium:

Clinical Condition	*Mechanism of Shift in Potassium*
1. Any chronic renal disease with decreased glomerular filtration.	1. Renal retention due to decreased glomerular filtration.
2. Upper and lower nephron nephrosis, acute stage.	2. Renal retention (back diffusion through tubules into blood).
3. Any state associated with severe dehydration (as untreated diabetic acidosis).	3. Hemoconcentration.
4. Untreated Addison's disease.	4. Hemoconcentration plus renal retention.
5. Excess potassium intake plus impaired renal function.	5. Renal retention.
6. Burns.	6. Shift from cells to serum (changes in cellular permeability and hemolysis).
7. Acute ischemia of muscle mass.[40]	7. Rapid tissue breakdown with liberation of nitrogen and potassium. Some degree of renal failure (?).

TABLE 3.—*Familial Periodic Paralysis* (The patient, a man 25 years of age)

Day	Hour	Serum Potassium Mg. per 100 cc.	RBC Potassium Mg. per 100 cc. cells	Urine Potassium Mg. per 100 cc.	Treatment Oral KCl Gm.	Clinical State
1	0					Operation
	11					
	18					Quadriplegia
2		6.3	350	16.6	2	Quadriparesis
3		17.2	.....	208.0	4	Weak
4		19.2	354	498.0	2	No weakness

changes reported in the literature, correlated and illustrated by the authors' material, is given.

Low Serum Potassium Levels:

The symptoms and signs of low serum potassium include muscle weakness, irritability, paralysis, tachycardia (rarely bradycardia), dilatation of the heart with gallop rhythm, and electrocardiographic changes.

Weakness and paralysis of muscles associated with low serum potassium levels have been reported in familial periodic paralysis,[24] during the therapy of diabetic acidosis,[22, 30, 34] in some patients with chronic renal disease[4] and in desoxycorticosterone acetate therapy of Addison's disease.[47] In some of these patients death has occurred due to paralysis of the respiratory muscles. Three deaths due to respiratory failure, associated with low serum potassium levels, occurred at the Los Angeles County General Hospital from September 1947 to January 1949. An autopsy was performed on each patient.

CASE 1: A boy, aged 15 years, entered the hospital with a ruptured cecum and generalized peritonitis. He had nasogastric suction and parenteral feedings for nine days. Vomiting and severe diarrhea occurred after normal feeding was resumed. Respiratory paralysis developed and the patient died. The serum potassium level was 5.3 mg. per 100 cc.

CASE 2: A girl one year of age entered the hospital with diarrhea and died of respiratory failure. The serum potassium level was 7 mg. per 100 cc.

CASE 3: A girl, aged 17 years, entered the hospital with diabetic acidosis. Following intensive therapy of the diabetic acidosis respiratory paralysis developed, with a serum potassium level of 8 mg. per 100 cc., and the patient died despite use of a respirator and parenteral potassium therapy.

These deaths, all in young individuals, stress the potential importance of very low serum potassium levels (under 10 mg. per 100 cc.).

The relationship of low serum potassium levels and muscle paralysis and weakness is illustrated further by the case of a patient with familial periodic paralysis (Table 3): Following operation for traumatic injury to the eye, quadriplegia developed. Shortly thereafter the serum potassium level was 6.3 mg. per 100 cc. As the serum level returned to normal there was complete recovery of muscle strength. It is to be noted that the urinary excretion of potassium was very low during the stage of paralysis, with gradual increase following oral potassium therapy. No shift of potassium into the red cells occurred. The potassium shift from the serum in this disease is suggested to be into the liver cells.[24] The muscle paralysis related to low serum potassium levels, as observed in this patient, usually affects first the muscles of the trunk and extremities, in contrast to myasthenia gravis, in which involvement of the cranial nerves is most striking. Involvement of the cranial nerves and sensorium is rare with potassium deficits, and if it occurs it is a late phenomenon. The electrocardiographic changes typical of low serum potassium, with return to a normal pattern as the serum concentrations reached normal (Chart 3), were noted in this case.

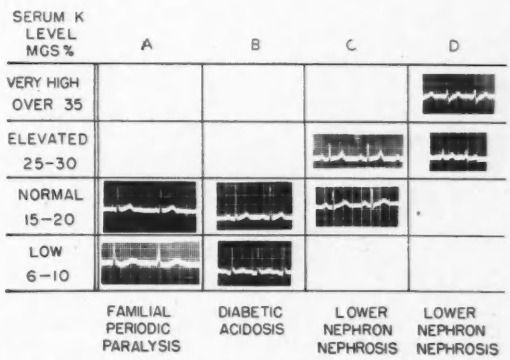


Chart 3.—Electrocardiographic changes associated with serum potassium changes.

There has been considerable disagreement in the literature about the relationship of low serum potassium levels and muscle weakness or paralysis. Some observers feel that there is no direct correlation.[5, 29, 37] It is to be noted that many of the patients with potassium deficits are critically ill with the primary disease and do not recognize muscle weakness, as such, unless it progresses to frank paralysis. If these patients are carefully examined, muscle weakness frequently can be detected. Further, it has been possible often to predict low serum potassium levels on the basis of the muscle weakness alone. It is the clinical impression of the authors that patients with serum potassium levels under 12 mg. per 100 cc. show some degree of muscle weakness. Striking improvement in muscle strength has been noted as potassium deficits alone have been corrected. Dynamometer studies have been reported by Harvey[29] in one patient during the therapy of

diabetic acidosis, with striking correlation of low serum potassium level with decreased muscle strength. Further studies of this type are indicated as a more objective method of evaluating muscle strength.

Generalized muscle irritability has been present in a few patients with potassium deficits.

The cardiovascular changes related to low serum potassium may be divided into clinical signs and electrocardiographic changes. Tachycardia was a prominent feature in most patients with serum potassium levels under 10 mg. per 100 cc. who were observed by the authors. This persisted in some after correction of the serum potassium deficit. Only one of the patients (familial periodic paralysis) had bradycardia. Bradycardia has been reported by others as an effect of low serum potassium in familial periodic paralysis.[39] It may be due to vagal effect. In some patients dilatation of the heart, systolic murmurs, and gallop rhythm developed. These signs, which usually disappeared rapidly with correction of the potassium deficit, suggest at least functional myocardial impairment. Elevation of the blood pressure has been reported associated with low serum potassium levels occurring during the therapy of diabetic acidosis.[22] This correlation was not noted by the authors in a study of potassium changes in a large number of patients with diabetic acidosis.

The electrocardiographic changes associated with low serum potassium have been well documented[35, 48] and need to be reviewed only briefly. Low serum potassium levels are associated with delayed A-V conduction (the authors have not seen this change), prolonged QT intervals and inverted, very low amplitude or flat rounded T waves. With correction of the serum potassium level, these changes usually revert to normal. These changes are illustrated in Chart 3 "*a*" and "*b*," which show flat rounded T waves in familial periodic paralysis and flat, low amplitude T waves in diabetic acidosis, both associated with serum potassium levels under 10 mg. per 100 cc. The QT interval is prolonged in both instances. The tracings reverted to normal as the serum potassium level became normal.

High Serum Potassium:

The symptoms and signs of high serum potassium levels are usually masked by uremia but may include bradycardia, dyspnea, coma and shock. The patients with potassium levels over 35 mg. per 100 cc. who have been observed by the authors have all died rapidly of cardiac standstill. Respiratory or muscle paralysis has been reported by several authors[20, 29] as occurring both due to high and low serum potassium. Harvey[29] suggests that the important feature is the imbalance between serum and cellular concentration. No instance of muscle paralysis due to high serum potassium has been noted in the series observed by the authors. The electrocardiographic changes associated with high serum potassium levels are striking and are illustrated in Chart 3. Between serum potassium levels of 25 and 30 mg. per 100 cc. the T waves become tall and peaked ("*c*"—lower nephron nephrosis). At about 35 mg. per 100 cc. the P waves disappear and the QRS complex widens ("*d*"—lower nephron nephrosis). With the potassium level between 40 and 50 mg. per 100 cc., the ventricular complexes become increasingly bizarre, with development of ventricular fibrillation (not illustrated). The changes in the electrocardiogram with high serum potassium have been discussed by many investigators.[20, 46, 48]

DIAGNOSIS OF POTASSIUM DEFICITS OR EXCESSES

The diagnosis of potassium changes rests on three principles:

1. *The recognition of clinical conditions* which potentially can alter the serum potassium level. These include conditions which alter potassium intake, or change in the potassium output from the body via the urine or from the gastrointestinal tract, and drugs or metabolic lesions which can cause shifts between cells and serum or serum and cells.

2. *A recognition of clinical signs of potassium deficits*, such as muscle weakness, paralysis, or irritability, and cardiovascular effects (dilatation of the heart, gallop rhythm, in conjunction with electrocardiographic changes).

3. *Determination of serum levels, and serial electrocardiograms.* Serial electrocardiograms may be very useful where serum potassium levels cannot be obtained. Some electrocardiograms are so striking that a diagnosis can be made on one tracing, but in general, serial tracings are necessary.

TREATMENT

Low Serum Potassium:

The problem of therapy for potassium deficits divides itself into three categories:

1. Prophylaxis, where possible, of potassium loss.

2. Treatment of the underlying cause of potassium loss, as diarrhea.

3. The immediate treatment of the serum potassium deficit.

In situations which are known to cause low serum potassium, it would be advantageous to prevent changes. Potassium should be added to intravenous solutions if a patient has to be maintained for more than a few days on them. Three to four grams of potassium chloride daily will prevent serious potassium deficits.

Treatment of the underlying causes of potassium deficit, as diarrhea, diabetic acidosis, etc., requires little comment.

The following plan for correction of potassium deficits has now been used in several hundred patients at the Los Angeles County General Hospital, without mishap. It is the policy to give potassium to all patients with serum potassium levels under 12 mg. per 100 cc. whether there are obvious symptoms or not. Potassium is not administered to any patient with dehydration until the dehydration is at least

partially corrected. No potassium is given if there is oliguria or anuria. Unless the clinical situation is urgent, two to three days is taken to correct potassium deficits. Where possible, the oral route of administration is used.

For oral administration, enteric-coated tablets of potassium chloride (0.3 gm.) and a 1 per cent solution of potassium chloride have been used. The solution is preferred, as the enteric-coated tablets have been found occasionally in the stools unchanged, and frequently it has been necessary to give the material to a patient through a Levine tube. With the use of a 1 per cent solution there has been little irritation, although occasionally diarrhea has developed. The amount used depends on the serum level and the primary disorder. For adults, between 4 and 12 gm. of KCl daily is given orally in divided doses until the serum deficit is corrected. Potassium chloride can also be given as a retention enema (5 to 10 gm. as a 1 per cent solution).

Potassium for intravenous or subcutaneous administration has been given as a 0.1 per cent solution of KCl (occasionally as a 0.2 per cent solution). Potassium chloride is prepared in vials (1 gm. in 15 cc. of distilled water), sterilized and then added to 1,000 cc. of parenteral fluid (as isotonic saline, glucose in water or saline, amigen, ammonium chloride). The liter of fluid is then given slowly over a period of two to three hours. With this dilution and time of administration there is little danger of too rapid shift of the serum level. Potassium chloride in 0.1 per cent strength is nonirritating. Several observers have reported the use of 1 to 2 per cent potassium chloride intravenously.[30, 43] These concentrations are hypertonic, and frequently cause severe pain and spasm of the vein. The volume of fluid is small and if care is not taken it may be given too rapidly. Darrow's solution, which is commercially available, contains potassium chloride, but also contains sodium. Because it is frequently necessary to administer potassium without sodium, the separate solution is preferred. In general, where intravenous or subcutaneous administration is required 2 to 4 gm. of potassium chloride is given daily, unless there are acute symptoms of potassium deficit; in that event, much more may be necessary, and a more concentrated solution is used. Where large amounts of potassium need to be given intravenously, serial electrocardiograms are helpful in following serum potassium concentrations. Potassium is given until the electrocardiogram tracings, particularly the T waves, become normal (see case reported by Harvey[29]). In this way toxic levels can be prevented.

Results of therapy are shown in Table 4. The fact that dosage for correction of serum levels varies widely is demonstrated. In Case 2, 13 gm. of potassium chloride (10 gm. by retention enema and 3 gm. subcutaneously) raised the serum level from 9 to 20 mg. per 100 cc. in one and one-half days, while in Case 5, 17.4 gm. raised the level only from 13 to 17 mg. per 100 cc. in two days. The various routes of administration are also shown in Table 4.

Further results of therapy are shown in Table 5. This table gives the serum potassium levels in four patients treated for diabetic acidosis as indicated. Two patients received potassium therapy and two received none. It is noteworthy that the patient (Case 2) who received the largest amount of potassium and also intravenous glucose had no fall in serum potassium level. Further evidence that intravenous glucose is not the only factor in the fall of serum potassium level, as suggested by some,[43] is seen in Cases 1 and 4 (Table 5). Both patients had pronounced fall in serum potassium level during the first 24 hours of insulin therapy. One received a large amount of intravenous glucose (240 gm.), and the other only a small amount of glucose (50 gm. subcutaneously). One patient (Case 3) received no intravenous glucose, but did receive a large amount of potassium, and the serum potassium level was maintained. From a study of potassium therapy and potassium deficits in 50 patients in diabetic acidosis[34] the authors feel that large amounts of intravenous glucose do accelerate the fall in serum potassium, but are not the only factor. Several articles[22, 30, 43] have given the impression that 1 to 2 gm. of potassium salt intravenously or orally would correct the potassium deficit in diabetic acidosis. The retention of potassium in the patients reported by Danowski[9] and co-workers indicates that much larger amounts are usually necessary. Harvey[29] also reported giving 33 gm. of potassium in 15 hours to correct paralysis occurring in one patient during

TABLE 4.—*Results of Therapy of Low Serum Potassium Levels*

Case No.	Age and Sex	Diagnosis	Mg. per 100 cc. Serum Potassium	Time	Gm. KCl	Route
1.	63 F.	Diabetic acidosis	9.2 to 20	1 day	12	Oral.
2.	62 M.	Pyloric obstruction	9.0 to 20	1½ days	13	Retention enema & subcut.*
3.	67 M.	Gastroenterostomy	8.0 to 13.4	2 days	14	I.V.† and Oral.
4.	49 M.	Bleeding peptic ulcer	9.0 to 15	2 days	8	I.V. and Subcut.
5.	13 M.	Ruptured appendix	13 to 17	2 days	17.4	I.V. Subcut. and Oral.
6.	35 F.	Acute pancreatitis	9 to 13 11 to 13	2 days 4 days	7 22	I.V. Oral.

* Subcut.—Subcutaneous. † I.V.—Intravenous.

TABLE 5.—*Treatment of Diabetic Acidosis*

Case No.	Sex and Age	Serum Potassium 0 hr. Mg. per 100 cc.	Serum Potassium 24 hr. Mg. per 100 cc.	Intake Potassium Gm.	Urine Output Potassium Gm.	Balance Potassium Gm.	Intravenous Glucose Gm.	Insulin Units
1.	F. 63	19.9	9.2	0	1.84	—1.84	240	400
2.	M. 26	16.5	16.0	9.14	4.70	+4.44	100	225
3.	F. 77	22.2	24.5	6.80	0.97	+5.83	0	205
4.	F. 29	22	13.6	0.35	1.73	—1.38	50 Subcut.	210

therapy of diabetic acidosis. The authors' results, as illustrated by the examples in Table 5, also indicate that large amounts of potassium may be necessary. It is now routine practice with the authors to give all patients in severe diabetic acidosis, if renal function is adequate, 1 gm. of potassium chloride in 1 liter of isotonic saline intravenously at the fourth hour of therapy, and 12 gm. of potassium chloride orally, in divided doses, during the first 24 hours, starting at the fourth hour. The first dose is given intravenously, as several patients have been observed who had critically low serum potassium levels, despite severe dehydration, at the time of admission to the hospital.

High Serum Potassium:

The treatment of high serum potassium is also important, as it can be as lethal as low serum levels. To date less attention has been directed to this problem. Many patients dying in uremia actually die of the effect of high serum potassium. If the renal lesion is a potentially reversible one, as is true in many cases of upper or lower nephron nephrosis, reduction of the serum potassium level may be lifesaving. Several methods have been advocated: Glucose and/or insulin[6, 25] to shift the potassium into the cells, large saline infusions to wash out potassium[42] in the urine or correct extracellular sodium deficits,[20] calcium to antagonize potassium effect on the heart,[49] peritoneal[42] lavage or artificial kidney[32] to clear potassium from the serum. The authors have used insulin and glucose in three patients for 12 to 24 hours, with only slight reduction in the serum levels (2 to 6 mg. per 100 cc.). It is difficult to shift potassium by this method into cells which contain a normal or increased content of potassium. Large saline infusions have not been used, as the majority of patients with high serum potassium levels were oliguric or anuric. With gastric lavage the serum potassium level was decreased from 34 to 26 mg. per 100 cc. in one patient; it was lowered from 25 to 22 mg. per 100 cc. with peritoneal lavage in another patient. Further work is needed on methods of reducing high serum potassium concentrations.

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Acute Pancreatitis

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SUMMARY

Pain, and nausea and vomiting are the two cardinal symptoms of acute pancreatitis.

There are variations in the combinations of symptoms that appear in patients who have acute pancreatitis, but in most cases the combination fits one or another of five classifications.

Blood amylase and urinary diastase determinations are valuable aids in the diagnosis of acute pancreatitis. These findings must be correlated with the stage of the disease.

As the disease may be treated successfully (by means outlined) without surgical intervention, clinical diagnosis is important.

Cholecystograms after an attack of acute pancreatitis, although advisable, should not be made too soon after subsidence, because of the danger of exacerbation.

IN 1946 the authors[2] presented a statistical study based on 307 proven cases of acute pancreatitis from Los Angeles County General Hospital. This series represented all cases of proven acute pancreatitis occurring during the 13-year period to January 1946. A review of the cases occurring in this same institution from January 1946 to January 1949 has just been completed. This second series consists of 145 cases which were diagnosed in a three-year period as compared to the first series of 307 cases diagnosed during a 13-year period. This does not represent a total increase in incidence of the disease but, rather, a definite increase in recognition of the disease because of greater diagnostic alertness.

The purposes of this presentation are:

1. To emphasize the usual and unusual manifestations of the disease.[3]

2. To reemphasize the importance of non-operative treatment during the acute phase.

A statistical review of the latter series and the combined series will be published elsewhere later.

SYMPTOMS

The two cardinal symptoms of acute pancreatitis are pain, nausea and vomiting. A discussion of the pathological physiology of these two symptoms was presented in a previous publication.[3] The symptoms of acute pancreatitis may exactly simulate those of any condition producing acute abdominal distress. Usually the onset and course of the disease are such as to make the case fit one of the following five descriptions:

Group I. Sudden onset of severe, excruciating upper abdominal pain commonly occurring in an elderly, obese, florid male who has eaten a large meal several hours previously, preceded by several highballs. Immediately following the onset of pain, nausea and (usually profuse) vomiting occurs. The patient is in profound shock with cyanotic mottled skin, diffuse tenderness and minimal to severe rigidity of the abdomen. Ecchymosis or bluish discoloration in either or both flanks or about the umbilicus may subsequently occur. Death commonly follows in 48 to 72 hours in spite of all forms of therapy directed at control of acute pancreatitis. This is the usual textbook description of the disease, but fortunately this group represents only a small per cent of the cases. Into this group also fall those patients with symptoms simulating those of acute coronary occlusion with pain in the left upper quadrant of the abdomen or in the precordium.

The remaining four syndromes, which are representative of the more common forms of the disease, are not sufficiently emphasized in standard textbooks on surgery.

Group II. The syndrome simulates that associated with acute cholecystitis, with sudden onset of moderately severe epigastric or right upper quadrant abdominal pain which may radiate through to the back or around the right costal margin to the back. The onset of pain is followed by nausea and vomiting, usually moderate in amount, but sometimes profuse. Occasionally there may be associated mild or moderate jaundice, which further confuses the clinical diagnosis. Jaundice was present in 17 of the previously mentioned series of 145 cases.

This syndrome is representative of those cases of acute pancreatitis involving primarily the head of the pancreas. In such cases the patient, early in the course of the disease, may be relieved of symptoms by the use of right paravertebral block. (This will be further discussed under treatment.)

Group III. The symptoms are typical of acute mechanical small intestinal obstruction. The patient may have intermittent, generalized, rhythmic, cramp-like abdominal pain associated with nausea and vomiting, with both clinical and x-ray evidence

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of distention of the small bowel. Patients in this group usually present no obvious cause for the obstruction (such as an external hernia or abdominal scar), and commonly present is a physical finding which is normally not present in intestinal obstruction. This is flank tenderness, either unilateral or bilateral, which is caused by retroperitoneal extravasation of pancreatic fluid. In the past the largest number of mistaken diagnoses in the authors' series was among patients in this classification. It is now routine to determine blood amylase and urinary diastase in all cases of apparent mechanical small intestinal obstruction without obvious cause.

Group IV. The clinical picture is that of acute alcoholism with acute gastritis characterized by upper abdominal pain with nausea and profuse vomiting. These symptoms may be mild to severe. This group commonly includes cases in which the diagnosis is slow leaking peptic ulcer induced by a recent bout of alcoholism. Because of the known high incidence of acute pancreatitis associated with or during acute alcoholism, the diastatic activity is determined routinely at Los Angeles County General Hospital in any case in which an alcoholic patient is admitted with abdominal symptoms.

Group V. This group includes those cases in which the patient has a mass in the epigastrium or left upper quadrant of the abdomen. Such patients frequently give a history of having had an attack of abdominal pain with nausea and vomiting three or four weeks previously. This represents an attack of acute pancreatitis which has progressed into one of its complications, a pseudocyst, a collection of exudate in the lesser sac or, rarely, a pancreatic abscess.

ASSOCIATED SYMPTOMS

Diarrhea. In the first study reported, diarrhea was noted as having occurred in 22 of 307 cases. In the more recent study it occurred in 17 of the 145 cases. Patients with diarrhea may have associated cramp-like abdominal pain, with nausea and vomiting—symptoms which often cause confusion with the syndrome of acute gastroenteritis or enterocolitis. The authors will probably ultimately classify patients with this combination of symptoms in an additional bracket, group VI, but at present the number of cases is too small to justify such a grouping.

Gastrointestinal Hemorrhage may be associated with acute pancreatitis. Its presence may be manifest in blood in the vomitus or in bloody diarrhea. This is not common, but it occurred in both series studied by the authors. There was no previous report of it in the literature.

DIAGNOSIS

The diagnosis can usually be made from the history, as most cases will fall into one of the previously described groups. The physical findings vary considerably according to the stage of the disease and the severity of the process. Practically all patients have moderate to severe abdominal tenderness, most pronounced in the epigastrium, right upper quadrant or left upper quadrant of the abdomen. Later in the disease there may be diffuse abdominal tenderness after the extravasation of bloody fluid from the pancreas into the peritoneal cavity. The patients commonly have unilateral or bilateral flank tenderness, which is rarely present in other acute conditions of the abdomen. There may also be a bluish discoloration or ecchymosis in either flank (Turner sign[6]). Rarely a bluish discoloration or ecchymosis about the umbilicus (Cullen's sign[1, 7]) may be present.

Diastatic Activity. The blood amylase becomes elevated within the first 24 hours in acute pancreatitis, but frequently remains normal for the first 12 to 18 hours. The amylase then remains elevated for 24 to 72 hours, depending upon the severity of the disease, but frequently returns to normal before clinical subsidence of the process. The urinary diastase commonly does not increase until 24 hours after the increase in blood amylase, but remains elevated 24 to 48 hours longer than the amylase. As these time elements are not constant and the reverse may occur, the authors recommend the simultaneous use of both tests in any suspected case of acute pancreatitis.

Roentgenologic Study. A plain film of the abdomen in acute pancreatitis is rarely diagnostic. It may show a segmental ileus of any section of the gastrointestinal tract, but this occurs most frequently in the transverse colon.

Blood Calcium. Blood calcium may be lowered due to the utilization of the ionizable calcium which combines with the fatty acids in the formation of calcium soaps, a process indicated by characteristic areas of fat necrosis. Recognizable lowering of the calcium occurs, however, only in the moderate and severe stages of the disease. A low level of calcium is probably most useful in diagnosis in the case of patients in the late stage of the disease, after diastatic activity has returned to normal.

TREATMENT

The treatment of choice in uncomplicated acute pancreatitis is non-surgical. The authors believe this to be extremely important in view of the mortality rate in the first series[2] reported and even more striking data in the current series. For this reason, it is important that physicians be alert for acute pancreatitis so that the diagnosis may be made clinically rather than at the time of surgical exploration.

Basic in the conservative treatment of acute pancreatitis is to put the pancreas as nearly at rest as is physiologically possible. To this end, treatment should include: (1) Continuous nasogastric suction; (2) adequate sedation; (3) adequate and regular use of atropine sulfate; (4) sufficient parenteral fluids to maintain water and electrolyte balance; (5) possible arterial antispasmodics. Following the work of Trueta[4, 5] in regard to the possible role of arterial spasm, the authors have been using paravertebral blocks, either unilateral or bilateral, depending upon the clinical location of the disease.

Intravenous novocain was used,* and more recently epidural block. Epidural block has certain advantages: It requires the use of only one injection site, and it interrupts the sympathetic as well as the sensory fibers, which gives the patient immediate relief of pain. Splanchnic block is also effective.

The use of continuous nasogastric suction produces several desirable effects: (1) Gives the patient symptomatic relief by controlling vomiting; (2) prevents the acid gastric secretions from entering the duodenum, thus reducing the hormonal stimulation of the pancreas to a minimum; (3) prevents acute gastric dilatation and helps control ileus. One important factor in the non-surgical treatment is to continue nasogastric suction for at least 24 hours after the temperature has returned to normal. When the suction is discontinued too early, acute exacerbation commonly occurs.

The fluid and caloric requirements are met by giving 3,000 to 4,000 cc. of 5 per cent glucose solutions daily. No insulin is given unless there is associated diabetes. In cases in which prolonged nasogastric suction is necessary, frequent determinations of the carbon dioxide combining power, blood sodium and potassium are made.

Atropine sulfate is given in large doses, 0.6 mg. to 0.8 mg. regularly every three to four hours. This is done to suppress the vagus effect on the pancreas. Vagus stimulation produces pancreatic juice rich in enzymes. Atropine also produces some degree of relaxation of the sphincter of Oddi. Morphine sulfate, 10.0 mg. to 15.0 mg., is given regularly to control the pain of pancreatic necrosis. The morphine also decreases the activity of the gastrointestinal tract. Penicillin given in doses of 25,000 to 100,000 units every three to four hours has been used in a small number of cases. The authors are not yet prepared to state the effectiveness of this drug in acute pancreatitis, as the number of patients treated with it is too small to have statistical significance.

Although it is felt that a cholecystogram should be made routinely following an attack of acute pancreatitis, in several cases acute exacerbation developed immediately following cholecystogram. Therefore, the authors now postpone this procedure until at least eight weeks after an acute attack.

* At the suggestion of C. J. Berne, M.D.

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Chronic Relapsing Pancreatitis

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SUMMARY

Chronic relapsing pancreatitis is a disease of recurring acute episodes of severe upper abdominal pain which are progressive and gradually may become so severe and so frequent as to be intractable.

Early in the disease the function of the gland and of the islet tissue may be disturbed only at the time of the acute attack, but subsequently these changes may become permanent and manifested by steatorrhea, creatorrhea and diabetes mellitus. The results of studies of pancreatic function parallel those of the pathologic process, and calcification of the pancreas is common.

Medical treatment is generally disappointing. Paravertebral injections may control acute pain. Surgical therapy is none too satisfactory. Long continued biliary drainage, anastomosis between the common bile duct and duodenum and between the pancreatic duct and duodenum, section of the sphincter of Oddi, partial and total pancreatectomy and sympathectomy, splanchnicectomy and vagotomy have been helpful in relieving pain and in preventing the recurrence of attacks in some instances.

MUCH interest in acute and chronic inflammatory diseases of the pancreas has been aroused in recent years, owing largely to excellent clinical and pathological descriptions by Comfort and his associates, and to increasing experience of various surgeons with partial and total pancreatectomy and with injections of or resections of nerves in the control of the painful seizures of these diseases. Diseases of the pancreas, with the exception of those manifested by diabetes mellitus or by advanced carcinomatous changes, have generally been difficult to diagnose clinically because of the inaccessible anatomic location of the organ and of the lack of satisfactory simple tests of pancreatic function.

Various apparently unrelated forms of acute and chronic pancreatitis have been described over a period of many years, but a clear-cut clinical concept of an entity now frequently called "chronic relapsing pancreatitis" was not developed until Comfort, Gambill and Baggenstoss in 1946 presented their studies of 27 such cases. They pointed out that this disease manifests itself by recurring attacks of pain, usually in the upper part of the abdomen, by disturbances of function of acinar and islet cells, and by certain sequelae.

Chronic relapsing pancreatitis is not a common disease (approximately 20 cases were encountered each year in the early 1940's at the Mayo Clinic) but it is now more frequently recognized than it was formerly. Curiously, it predominates in the male (6:1), and patients who have the disease are usually not obese. In these last two respects it differs from disease of the biliary tract. It is more common in patients in middle age (median 37 years) and in alcoholics.

ETIOLOGY AND PATHOLOGY

The cause of chronic relapsing pancreatitis is not clear and there has been wide discussion of the relation of it to disease of the gallbladder, bile ducts, and liver. Recent studies of Gambill, Comfort and Baggenstoss have indicated that the clinical picture, pathologic physiology, the course of the disease and the pathologic alterations in the pancreas in cases of chronic relapsing pancreatitis are very constant, regardless of the presence or absence of disease of the biliary tract. These findings, as well as the differences between the two diseases with regard to sex incidence and the presence of obesity, strongly suggest that pancreatitis is not necessarily secondary to disease of the biliary tract but may be and frequently is independent of it.

Baggenstoss has shown that grossly the pancreas, in cases of chronic relapsing pancreatitis, is indurated and sometimes nodular, and that, microscopically, fibroblastic proliferation and fibrosis are prominent features. Gross atrophy of the gland, pseudocyst formation and macroscopic calcification are characteristic of the disease. Interstitial fibrosis and residual necrosis of tissue are other constant findings. Fibrosis is usually interlobular, although intralobular and intra-acinar fibrosis occur. Infiltration with lymphocytes and plasma cells is common, but actual suppuration is rare. Insofar as associated changes in the bile ducts are concerned, it appears that this form of pancreatitis may be responsible for dilation of the gallbladder, and that the degree of pathologic change in the gallbladder and ducts bears some relationship to the extensiveness and activity of the disease in the pancreas.

SYMPTOMS

Recurring, acute, severe, prolonged exacerbations of upper abdominal pain, separated by intervals of

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relative or complete clinical quiescence, are characteristic of the disease. Pain is the outstanding clinical feature of the acute attack. The pain may begin gradually or suddenly, is generally in the upper abdomen, is severe, is prolonged (from several hours to several days), is variable in type but usually steady, and frequently and characteristically it radiates to the left upper quadrant of the abdomen and to the back. Often, repeated doses of opiates are needed for relief, and not infrequently the patients become addicted to opiates. The interval between attacks varies greatly; it may be years in the early stages of the disease. Usually as the disease progresses the intervals shorten and become marked by persisting digestive symptoms, signs of disturbance in pancreatic function, and at times by diabetes mellitus. In short, the disease tends to be progressive, the attacks becoming more frequent, more prolonged and more severe.

Accompanying the pain are variable symptoms of gastrointestinal dysfunction such as nausea, vomiting, constipation or diarrhea, abdominal distention, jaundice, bleeding and such general symptoms as weakness, fever, sweating and shock.

In the interval between attacks there are frequently no symptoms in the early stages of the disease. Later on, various non-specific clinical syndromes may develop with symptoms including intolerance to fatty foods, flatulence, weakness, constipation, anorexia and epigastric distress.

In approximately half of the cases observed by Comfort, Baggenstoss and Gambill, pronounced permanent sequelae including diabetes, steatorrhea and calcification of the pancreas were present and observable in the interval between acute painful exacerbations of the disease.

DIAGNOSIS

The diagnosis of chronic relapsing pancreatitis may be simple in a typical case when all of the characteristic features are present. On the other hand it may be extremely difficult in the patient whose only manifestation of the disease has been recurring attacks of upper abdominal pain.

The most useful diagnostic feature in the history is that of recurring, severe, protracted upper abdominal pain with features previously noted. Associated symptoms excepting jaundice are usually non-specific and in keeping with any severe abdominal pain due to an acute inflammatory process. Addiction to opiates may be present.

Physical examination during an attack may reveal moderate fever, epigastric tenderness and rigidity and jaundice. "The appearance of a rounded cystic mass in the pancreatic region during the painful seizure or soon thereafter may have the same significance as does diabetes mellitus, steatorrhea or calcification." (Gambill and co-workers.) In the interval between attacks examination may disclose no abnormality except for evidence of weight loss and epigastric tenderness.

Laboratory data obtained during an acute attack may reveal leukocytosis, acceleration of the sedimentation rate and evidence of jaundice. Glycosuria and transient hyperglycemia are infrequent unless diabetes mellitus is present. The following phenomena, if present, are useful in substantiating the diagnosis: Elevation of values for amylase and lipase in the serum and of the value for fecal solids, fat and nitrogen in the stool by chemical analysis, grossly fatty stools and excessive amounts of fat by microscopic examination. Even during an acute attack, however, results of tests mentioned may be within normal limits. In some cases in which accurate studies can be made of the volume and of the bicarbonate and enzymatic concentration of duodenal content after stimulation with secretin, the finding of values lower than normal may be useful to substantiate the diagnosis. Negative results of tests do not exclude the disease.

Roentgenologic studies are useful in ruling out other causes of severe abdominal pain in the stomach, duodenum, colon and gallbladder. They may also reveal multiple areas of calcification throughout the pancreas and, in fact, the gland may appear largely calcified. Abnormalities in the appearance of, or in the peristaltic activity of the stomach or duodenum in those areas where they are contiguous with the pancreas, may be a useful confirmatory diagnostic help in an occasional case.

Finally, the course followed by the patient may be diagnostically important because it may be typical —recurring acute, severe, prolonged, upper abdominal pain associated with transient elevations in value of serum lipase or amylase, and perhaps hyperglycemia and glycosuria during the attack, generally followed over a period of years by more severe and more prolonged attacks of pain, by prominent physiological alterations in glucose metabolism and by development of steatorrhea and creatorrhea. Such a pattern generally establishes the diagnosis. If in addition radiological evidence of calcification of the pancreas is found, the diagnosis is clear.

In many patients with this disease the diagnosis is not established until operation is performed. In fact, in over half the cases the correct diagnosis is not made preoperatively. It is particularly liable to be missed in those cases in which symptoms resemble those of biliary tract disease — namely, jaundice and colics—and there is no laboratory evidence of pancreatic disease.

TREATMENT

Treatment of the attack of acute pancreatitis is generally considered a medical problem, whereas surgical treatment may be advisable and helpful in managing the patient with recurring attacks of pain or with associated disease in the biliary tract.

Medical: Medical treatment of the acute attack is largely symptomatic and consists of administration of ephedrine sulfate, papaverine hydrochloride or opiates, and of intravenous administration of fluids, of decompression of the upper gastrointestinal tract and control of shock if these measures are necessary.

Between episodes and when the disease becomes chronic, medical treatment consists of high caloric, high carbohydrate, low fat diet, control of diabetes if it is present, and avoidance of alcohol. Extract of the whole pancreas in doses of 5 gm. in enteric-coated tablets with each meal may help greatly in reducing abdominal discomfort and increasing absorption of food.

Surgical: In discussion of surgical treatment of chronic relapsing pancreatitis, consideration must be given to the end to be accomplished. The principal problem may be any of the following: To relieve the acute attack of pain, to attempt to prevent recurrence of severe attacks of pain, to improve pancreatic function, to relieve accompanying jaundice, or to remove associated disease of the biliary tract.

For the control of pain in the immediate attack, paravertebral block, with novocain, of the sixth to tenth dorsal segments has been advocated by deTakats and Walter, White and Smithwick, and others. Properly carried out, this method appears to be very effective, although it may have to be repeated several times during an acute episode. While this method of treatment would appear largely to control pain only and not to influence the disease process in the pancreas, some advocates of it believe that because spasm of the sphincter of Oddi may be relieved, promoting drainage from the pancreas, the method may actually affect the pathologic process.

Other more time-honored surgical methods of control of acute attacks, as well as of the lesion, include cholecystostomy with prolonged drainage and cholecystectomy with prolonged (six to 12 months) drainage of the common bile duct by a T-tube. It must be readily appreciated, however, that when drainage of the biliary tract is discontinued the pathologic process of the pancreas may progress and symptoms reappear.

Surgical procedures which have been recommended to control recurrent attacks of pain and to improve pancreatic function, and which are therefore most useful in the earlier stages of the disease, include choledochoduodenostomy, which has been particularly advocated by Waugh, and section of the sphincter of Oddi. The latter method, which has recently been applied in 21 cases by Doubilet and Mulholland, is carried out by an approach through the common duct or by opening the duodenum and directly sectioning the muscle over a probe. The rationale of this procedure goes back to the original suggestion of Archibald, that spasm of the sphincter of Oddi in the presence of a common biliary-pancreatic passageway and reflux of bile into the pancreas is a significant etiologic factor in acute pancreatitis.

Two other surgical procedures advocated for the disease include anastomosis of the dilated pancreatic duct to the duodenum, as reported by Crile, and ligation of the pancreatic duct, which according to Martin and Canesco is a treatment of choice at the Johns Hopkins Hospital Clinic. Crile states that the anastomotic procedure has given relief to approximately 50 per cent of patients operated upon and is therefore not a specific cure. The other procedure, ligation of the duct, leads to atrophy of the pancreatic acini without accompanying atrophy of the islands of Langerhans.

Finally, for those patients with extensive disease of the pancreas, manifested chiefly by recurring, severe, almost uncontrollable pain, the two most commonly advocated procedures include partial or total pancreatectomy and section of the sympathetic and/or parasympathetic nerve fiber supplying the pancreatic area. Whipple recently (1946) collected reports of 12 cases of total pancreatectomy from the literature and added two of his own. While this a heroic procedure with a great morbidity and high mortality rate, it would appear to be justified in an occasional patient with intractable pain who is perhaps already diabetic. Before carrying out such an extensive procedure, consideration should be given to a less serious operation such as section of nerves. Crile, deTakats and Walter, and others, have advocated ganglionectomy on the right side (seventh to twelfth dorsal) with or without resection of the right splanchnic nerve. While Rienhoff and Baker have reported section of both splanchnic nerves and both vagi with striking relief of pain, there is question whether in all cases such an extensive surgical procedure is necessary.

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The Clinical Significance of Urinary 17-Ketosteroid Assays

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SUMMARY

The urinary 17-ketosteroids are a group of compounds derived from complex steroids produced by the adrenal cortex, testis, or ovary. The method of determining the amount excreted has been simplified so that it is available for routine diagnostic purposes. Usually the amount is increased in diseases in which there is hyperfunction of the adrenal cortex due to tumor or hyperplasia, and decreased in lesions that impair the function of the adrenal cortex.

Other conditions such as myxedema, eunuchism, gout, and arthritis may alter the excretion of the 17-ketosteroids. Low levels are also found in the young and in the aged. Case histories are presented to illustrate the findings in the following diseases: Tumors of the adrenal cortex with (a) masculinization, (b) Cushing's syndrome with virilism and, (c) hirsutism; as well as in gigantism with acromegaly, in gout, eunuchism, Addison's disease, myxedema, and severe panhypopituitarism.

RECENT progress in the understanding of steroid metabolism has made the assay of urinary neutral 17-ketosteroids an important test in the evaluation of certain clinical conditions related to the endocrine system. This review will attempt to analyze briefly the current concepts concerning the origin, nature, and significance of these compounds, and will illustrate by means of case reports most of the conditions in which there is a definite abnormality in the 17-ketosteroid excretion.

The steroids present in the urine can be divided into neutral, phenolic, and acidic compounds (Diagram No. 1). The acidic steroids represent the bile acids; the phenolic are mainly the estrogens. The neutral steroids contain metabolites from the testes or ovaries and from the adrenals. There are four important groups of compounds present in the adrenal cortex that give rise to neutral steroids in the urine. These are: (1) androgenic substances, (2) progesterone, (3) desoxycorticosterone, (4) corticosterone. The testicular hormone, testosterone, is the precursor of some of the neutral 17-ketosteroids in the urine.

The neutral steroids in the urine can be subdivided into the ketonic and the nonketonic fractions. The latter are relatively small in quantity and are usually derivatives of progesterone and desoxycorticosterone. The more important ketonic fraction is composed of the following: Isoandrosterone from the testis, dehydroisoandrosterone from the adrenal cortex, and androsterone and other complex steroids that are metabolites from both adrenal cortex and testis.

The basic principles underlying the assay of neutral urinary 17-ketosteroids are not complex.[5] However, the actual technique is moderately involved and requires careful attention to details. The steroid metabolites in the urine are rapidly converted by hydrolysis to the free compounds by boiling with a strong inorganic acid. The steroids are extracted from the urine by means of an organic solvent. In some techniques, hydrolysis and extraction may be performed simultaneously. The estrogens are removed from the extract by washing with a weak alkali. The remaining extract is dried, dissolved in alcohol, and assayed by reacting it with m-dinitrobenzene.[8] The red color resulting from this reaction is compared with the color produced by a known amount of dehydroisoandrosterone. This determines the total neutral 17-ketosteroid content of the urine. Instead of the chemical reaction, a biologic test for androgenic activity may be substituted; however, the neutral 17-ketosteroids include substances that are not androgens, so that a direct correlation between androgenic activity and 17-ketosteroid content is not always evident. If more accurate determinations are required, the extract is treated with Girard's reagent T to separate the ketonic from the nonketonic fractions. In the normal individual the amount of nonketonic material is not sufficient to require this complex procedure. The total ketonic portion can be measured by means of the m-dinitrobenzene reaction, or it can be treated with digitonin to separate the alpha from the beta compounds. Androsterone represents the major portion of the non-precipitable alpha 17-ketosteroids. The principal component of the digitonin-precipitable beta 17-ketosteroids is dehydroisoandrosterone, and it is derived only from the adrenal cortex. In urine from normal individuals the beta fraction rarely exceeds 10 per cent of the total amount of the ketonic ketosteroids. In males the hormones of the testis give rise to about one-fifth, and the hormones

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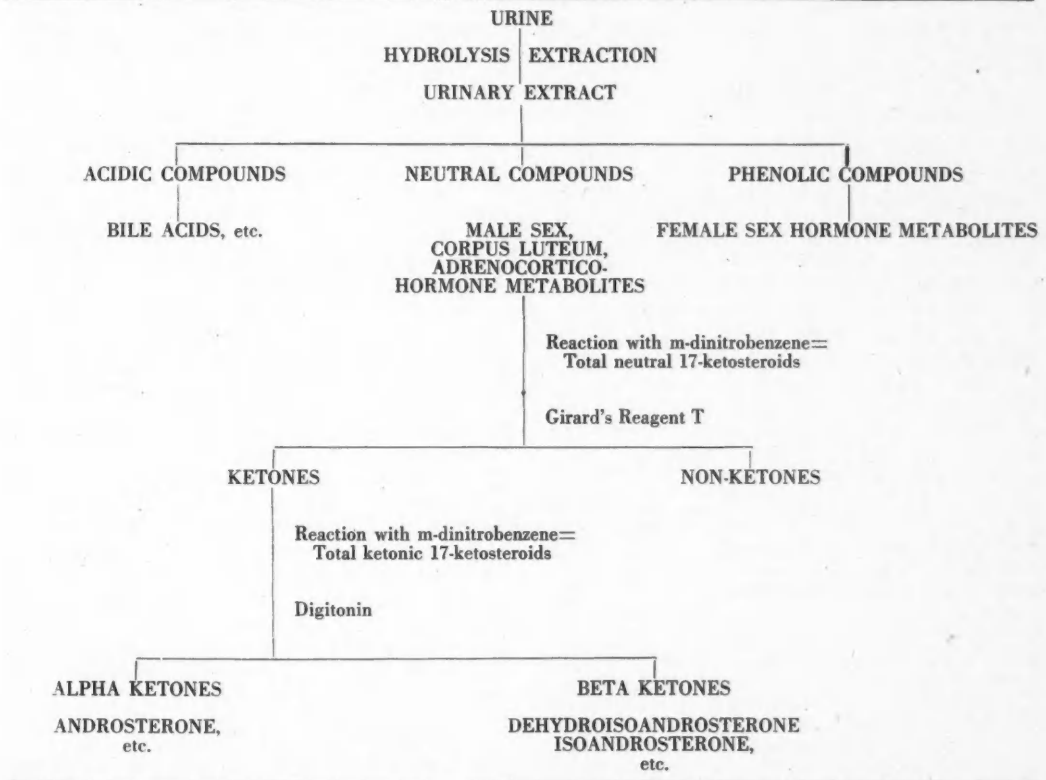
DIAGRAM No. 1



of the adrenal cortex to most of the rest of the 17-ketosteroid excretion. In females most of the 17-ketosteroids are derived from the hormones of the adrenal cortex.

The values for the 17-ketosteroids assayed in 24-hour urine specimens, obtained from adult normal individuals, fall within the following ranges: Males, 8 to 22 mg.; females, 6 to 13 mg. The amounts in children are variable. Up to two or three years of age none is present; from 3 to 8 years there may be as much as 2 mg.; from 8 to 12 years there are between 1.5 and 5 mg.; from 12 to 16 years the amount varies between 4.5 and 9.5 mg.

Increased amounts of 17-ketosteroids in the urine may be found in certain endocrine diseases. The most important and most common is the functioning tumor of the adrenal cortex. These tumors produce a variety of clinical syndromes that have been classified by Kenyon[4] into: (1) the adrenogenital syndrome; (2) Cushing's syndrome; (3) mixed clinical pictures having features common to the first two; (4) isolated expressions of the neoplasm; (5) feminization in adult males and rarely in children; (6) tumors without endocrine manifestations.

In instances of adrenal tumor with clinical evidence of intense masculinization, the 24-hour 17-ketosteroid excretion varied from 76 to 857 mg., and, where measured, the beta fraction varied between 30 and 79 per cent. In the reported cases, ten of the patients were females and one was a male.[2] The following case report lists an additional instance of typical masculinizing tumor of the adrenal cortex with an extremely high 17-ketosteroid excretion in which the beta fraction represented 25 per cent.

CASE REPORT*

CASE 1: The patient was a white female, 63 years of age, with clinical diagnosis of masculinizing tumor of the right adrenal gland. Virilization had begun 30 years previously, after the last pregnancy, characterized by increase in growth of hair on face and body, baldness, amenorrhea, muscular shoulders and arms, and enlargement of the clitoris to three times normal size. The systolic blood pressure was 200 mm. of mercury, the diastolic, 100 mm. The glucose tolerance test revealed the following blood sugar levels in mg. per 100 cc.: Fasting, 95; 30 minutes, 200; 60 minutes, 258; 120 minutes, 285; and 180 minutes, 219. Intravenous pyelograms showed no abnormality. A large encapsulated adenoma, 17.5 by 12 by 8.5 cm., that had replaced the right adrenal gland was removed on December 8, 1948, after inspection of the normal left adrenal gland and the atrophic pelvic organs. The following assays were performed:

Oct. 27, 1948: Total neutral 17-ketosteroids, 455.7 mg. per 24 hours.

* Courtesy of Roberto F. Escamilla, M.D.

Nov. 5, 1948: Total neutral 17-ketosteroids, 661.0 mg. per 24 hours.
Nov. 5, 1948: Total ketonic 17-ketosteroids, 663.0 mg. per 24 hours.
Alpha fraction, 571.0 mg.
Beta fraction, 170.0 mg. (25%)
Dec. 8, 1948: Surgical removal of adenoma of right adrenal gland.
Dec. 17, 1948: Total neutral 17-ketosteroids, 15.8 mg. per 24 hours.
Jan. 19, 1949: Total neutral 17-ketosteroids, 9.1 mg. per 24 hours.
Feb. 18, 1949: Total neutral 17-ketosteroids, 10.0 mg. per 24 hours.
Mar. 25, 1949: Total neutral 17-ketosteroids, 5.6 mg. per 24 hours.

In another case of masculinizing tumor of the adrenal cortex, the 17-ketosteroid excretion was elevated but not to such high levels:

CASE REPORT*

CASE 2: The patient, a white female 63 years of age, had a clinical diagnosis of masculinizing tumor of the left adrenal gland. In the preceding five years the patient had become bald with a masculine distribution of facial and body hair, and masculine musculature. A carcinoma of the right breast had been removed in 1944. At that time the blood pressure varied between 230 and 260 mm. of mercury systolic, and 125 and 142, diastolic. A 68-gram tumor was removed from the left adrenal gland on May 28, 1948. Subsequently the body hair slowly disappeared. The blood pressure remained elevated and at present there is evidence of hypertensive heart disease, early congestive failure, with fatigue and dyspnea, but no evidence of masculinization. The 24-hour total neutral 17-ketosteroid outputs were: May 15, 1948, 90 mg.; June 14, 1948, 1.5 mg.; April 18, 1949, 11.4 mg.

There are published reports of cases of tumors of the adrenal cortex that produced the Cushing syndrome and practically no virilism. In these cases the ketosteroid excretion paralleled that in the first group, varying from 19.9 to 800 mg., but in seven of the 13 cases reported, it was less than 75 mg. In three of the cases the beta fraction was less than 22 per cent of the total, but in two other cases the percentage was 65 and 69.[2]

There are 23 published reports of cases of tumor of the adrenal cortex in which there were masculinization and manifestations of Cushing's syndrome, and in these cases the excretion of urinary 17-ketosteroids was extremely variable but always above normal.[2] The following is a case that may be classified in this group:

CASE REPORT†

CASE 3: The patient was a white female, 39 years of age. The clinical diagnosis was Cushing's syndrome with virilism due to adrenal tumor. The following signs and symptoms were evident: extreme weakness of legs, moon face, plethoric countenance, exophthalmos, disproportionately thin extremities without obesity, easy bruising, amenorrhea, hirsutism, acne, hypertension (the blood pressure was 180 mm. of mercury systolic and 120 mm. diastolic), generalized osteoporosis, diabetic reaction to a glucose tolerance test, high 11-oxysteroids (2.92 mg.), and low eosinophil count. The total neutral 17-kerosteroid excretion was 62.4 mg. in 24 hours. The intravenous pyelograms showed no abnormalities, but perirenal gaseous insufflation revealed a tumor over the left kidney. The patient died on the fifth day of cardiac failure and pulmonary edema after surgical removal of an encapsulated tumor in the left adrenal.

There are instances of Cushing's syndrome that have been proved not to be due to a tumor of the adrenal cortex, and in those instances the 17-ketosteroid excretion varied between 7 and 37 mg. In at least half of the cases the amount extracted was within normal limits. In a few cases where the beta fraction was determined, it was 14 per cent or less.[2]

The assay of 17-ketosteroids offers some help in the differentiation of tumor from hyperplasia of the adrenal cortex. In the latter condition in females, there may be prepubertal virilism, often associated with pseudohermaphroditism or sex inversion, or postpubertal virilism that is characterized mainly by hirsutism. In the females in whom hirsutism develops after puberty, the 17-ketosteroid excretion is normal or does not exceed 37 mg. in 24 hours.[2] In the prepubertal cases, an increased excretion is more common, but it is usually under 100 mg. and the beta fraction is less than 23 per cent in 24 hours. In cases of tumor of the adrenal cortex with virilizing signs the excretion of 17-ketosteroids is often more than 100 mg. in 24 hours and the beta fraction is over 20 per cent. If in the presence of virilism there are, in addition, elements of the Cushing syndrome, there is usually a definite increase in the cortin content of the urine. In the following case, hirsutism that appeared in a girl at the age of 11 was the single endocrine expression of an adrenal tumor:

CASE REPORT‡

CASE 4: The patient was an Indian female, 28 years of age. The clinical diagnosis was hirsutism due to malignant adenoma of the left adrenal gland. The patient said that she had had excessive hair on the body since she was 11 years of age. An increased amount of hair over the chest, legs, and face, and a masculine distribution of pubic hair on the abdomen were noted. The voice was normal. The systolic blood pressure was 120 mm. of mercury, the diastolic 84 mm. Roentgenographic studies suggested a mass in the region of the left adrenal gland. The basal metabolic rate was plus 5 per cent. A malignant adenoma of the adrenal gland was removed Aug. 7, 1947. There has been relatively little change in the amount of body hair since the operation. Results of a series of total neutral 17-ketosteroid assays of 24-hour urine specimens were: May 7, 1947, 82.1 mg.; May 10, 62.2 mg.; September 11, 1947, one month after surgical removal of a malignant adenoma of the adrenal gland, 6.3 mg.; November 14, 10.2 mg.; February 4, 1948, 13.5 mg.; April 3, 19.2 mg.; August 10, 8.6 mg.

There are reports of nine cases of virilizing tumors of the ovary. In three of the cases the tumors were arrhenoblastomas, in three they were adrenal-like tumors, and in three the tumors were not described.[2] The patients that had arrhenoblastomas excreted 4.0 mg., 6.9 mg., and 56 mg. of 17-ketosteroids in 24 hours; the patients with adrenal-like

* Courtesy of Kendall B. Holmes, M.D., Fresno.
† Courtesy of Minnie Goldberg, M.D.
‡ Courtesy of Hans Lisser, M.D.

ovarian tumors excreted 17 mg., 23.8 mg., and 54.6 mg. In the other three cases excretion levels were 40 mg., 116 mg., and 158 mg. The excretion was measured after operation in four cases and in each it dropped to normal or subnormal levels.

There may be a subnormal, normal, or increased excretion of 17-ketosteroids in cases of acromegaly.[3] The following case report illustrates a combination of gigantism with early acromegaly:

CASE REPORT*

CASE 5: The patient was a white male, 41 years of age. The clinical diagnosis was eunuchoid gigantism with features of acromegaly. The height of the patient was 87 inches, the span 92 inches, and the weight 342 pounds. Roentgenograms revealed prognathism and slight tufting of the ends of the phalanges. There was atrophy of the testes. The 24-hour excretion of total neutral 17-ketosteroids was 9.2 mg.

The possible relationship of some diseases of the joints to the endocrine system has been suggested by the 17-ketosteroid excretion levels in gout and in spondylarthritis. A recently published report has brought out the fact that the 17-ketosteroid excretion is diminished in gout.[7] This has been confirmed in one case:

CASE REPORT†

CASE 6: The patient, a 31-year-old white male, with known polycythemia, had a first attack of gout on October 6, 1948. The blood uric acid concentration was 12.6 mg. per 100 cc. The patient was treated with colchicine. On October 26, 1948, neutral 17-ketosteroid excretion in the urine in a 24-hour period was 6.9 mg. Several attacks of gout occurred in the succeeding six months, and during one of these urate crystals were demonstrated in tophi.

It has been reported that in 31 cases of spondylarthritis in males the excretion of neutral 17-ketosteroids varied from 10 to 43.5 mg. The average was 26.7 mg. In four females with this disease outputs were 19.5 mg., 40 mg., 23 mg., and 16 mg.[1]

There is a significantly lowered excretion of 17-ketosteroids in the young and in the aged, as well as in persons with malnutrition, anemia, and chronic debilitating disease.[3] Severe physical stress produces an increased excretion that may be followed by a diminished output.[6] Acute trauma such as is produced by fractures, surgical operation, or the onset of acute febrile disease may be followed for a short time by a rise in 17-ketosteroid excretion. In some instances of chronic hepatic insufficiency the level is decreased. The administration of purified adrenocorticotropic hormone to normal males and females induces a distinct increase in the 17-ketosteroid excretion. In hypogonad males usually there is a diminished excretion[3] as is shown in the following report:

CASE REPORT‡

CASE 7: The patient, a white male, 55 years of age, had been surgically castrated following severe trauma at age 22. Since then he had had decreased libido, diminution in amount of beard, axillary and pubic hair, and loss of strength. Examination revealed recently acquired obesity, gynecomastia, pigmentation of the face with wrinkling of the skin, and normal blood pressure. The basal metabolic rate was zero, the cholesterol content of the blood serum was 222 mg. per 100 cc. The total neutral 17-ketosteroid excretion on two examinations was 3.3 mg. and 4.6 mg. in 24 hours.

There are three outstanding diseases in which there is a decreased excretion, often severe, of 17-ketosteroids. These are anterior pituitary insufficiency, Addison's disease, and myxedema. The 17-ketosteroid output in the presence of these diseases is usually less than 6 mg., the lowest levels occurring in the first two. In some instances urinary gonadotropin assays are required to distinguish between cases of primary hypophyseal disease with features of adrenal insufficiency and those of primary adrenal failure. Treatment of myxedema with desiccated thyroid usually does not elevate the subnormal excretion of 17-ketosteroids, nor does the maintenance of a patient in good clinical condition with Addison's disease by means of desoxycorticosterone and adrenal cortex extract.

The following case reports illustrate the clinical and laboratory findings in typical instances of these three diseases.

CASE REPORTS

CASE 8:* The patient was a white male, aged 42 years. The clinical diagnosis was panhypopituitarism: "burnt-out" acromegaly with hypogonadism, myxedema and severe Addison's disease. The patient entered the hospital in Addisonian crisis. Roentgenographic examination showed a large sella, tufting of the terminal phalanges and prognathism. The testes were atrophic, and biopsy revealed tubular degeneration. The prostate was minute. The skin of the face was fawn-colored. The basal metabolic rate was minus 24 per cent. Urinary excretion of the follicle-stimulating hormone was less than 5 mouse units in 24 hours. The urinary excretion of neutral 17-ketosteroids on March 24, 1948, was 2.6 mg. per 24 hours. The patient was treated for the acute Addisonian crisis and finally stablized on thyroid extract, testosterone propionate and 4 mg. of desoxycorticosterone acetate daily. On this regimen he returned to lumberjacking. The total neutral 17-ketosteroid excretion on April 29, 1949, was 2.1 per 24 hours.

CASE 9:† The patient, a white male, 49 years of age, with a clinical diagnosis of tuberculosis of the adrenal glands, entered the hospital in Addisonian crisis. The Robinson-Power-Kepler tests No. 1 and No. 2 showed positive results. The urinary excretion of neutral 17-ketosteroids on Dec. 7, 1948, was 1.2 mg. in 24 hours. The patient was treated in the usual manner and stabilized on salt and desoxycorticosterone acetate. After he had resumed normal physical activity, the 17-ketosteroid assay on February 7, 1949, was 4.2 mg. in 24 hours. He died unexpectedly and autopsy revealed bilateral caseous tuberculosis of the adrenal glands; direct extension of the tuberculous process from the left adrenal to the spleen, with miliary dissemination in the liver.

CASE 10:‡ The patient was a white male, 67 years of age, with clinical diagnosis of myxedema. He complained of extreme fatigue for the previous six months, coldness of the hands and feet, pain in the hands associated with stiffness, and a gain in weight of 20 pounds. On examination the skin

* Courtesy of Drs. Sanford E. Leeds and Morton J. Nyda.
† Courtesy of Harris M. Fishbon, M.D.
‡ Courtesy of Myron Arrick, M.D.

* Courtesy Veterans Administration Hospital, Ft. Miley, San Francisco.
† Courtesy of Russel F. Rypins, M.D.
‡ Courtesy of Roberto F. Escamilla, M.D.

was dry, the face was puffy and pale, there was swelling of the hands and feet, and the tongue was thick. The basal metabolic rate was minus 41 per cent. The cholesterol content of the blood serum was 333 mg. per cent, and the iodine level of the blood was 3.2 micrograms per cent. The total neutral 17-ketosteroid excretion was 4.8 mg. in 24 hours.

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Liquid Nitrogen in the Treatment of Skin Diseases

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SUMMARY

Liquid nitrogen is a satisfactory freezing agent in the treatment of such skin diseases as warts, keratoses, superficial hemangiomas, leukoplakia, keloids, superficial scarring and dermatitis venenata. It is available and easily applied. Its use is described and the results of treatment in 154 cases of warts are presented.

THERE have been several articles, the most recent one by Kile and Welch,[1] on the use of liquid gases as cryotherapeutic agents in dermatology. This presentation will briefly review some of the practical aspects of this method of treatment.

Liquid air was the first gas used and may still be used. It contains approximately 78 per cent nitrogen, 21 per cent oxygen, 1 per cent argon and traces of other rare gases.

In recent years the commercial demand for oxygen and nitrogen has led to the production of these elements in almost pure form and in tremendous quantities. The process of manufacture includes the compression and the refrigeration of atmospheric air and then its fractional distillation and chemical rectification.

Because of its easy availability liquid oxygen has been used for a number of years and still is often used. Recently, as liquid nitrogen has become more commonly available, it has partially replaced liquid air or liquid oxygen. It has the advantage of being largely inert and avoids the fire hazard inherent in liquid oxygen. Its only disadvantage is perhaps that it is approximately 13° C., or 7 per cent, colder than liquid oxygen and therefore is lost slightly more quickly by vaporization. This is of little practical importance, however.

The liquid nitrogen used in the Student Health Service clinic at the University of California, Berkeley, is obtained from the physics department in a quart-sized thermos bottle. This is surrounded by cotton waste and set in a plywood box measuring about eight inches square and 12 inches deep. The open mouth of the glass container is covered by a half-inch layer of orthopedic felt. Each clinic morning approximately a quart of the liquid nitrogen is obtained. This has been used in treating as many as 21 cases of warts during a clinic period. Much of the liquid nitrogen is left in the container at the end of the clinic.

For office use the author obtains liquid nitrogen—2.5 liters in a special 5-liter container—from a commercial source. From this container the nitrogen is poured as it is needed into a pint thermos bottle surrounded by cotton waste and enclosed in a small plywood box. This box is provided with a handle for ease in carrying it about the office. The supply is obtained twice a week, on Monday and Thursday mornings, and the rate of evaporation with this care is such that it is usually available continuously throughout the week.

The liquid nitrogen is applied by means of an ordinary cotton swab or applicator stick. In order to pick up the liquid nitrogen, it is important not to wrap the cotton too tightly on the applicator. This is dipped into the liquid and applied to the lesion to be treated. No appreciable pressure is required for most lesions, and freezing is almost instantaneous.

Lesions of considerable depth, such as warts on the palmar or plantar surfaces, require several seconds to become frozen to their whole depth. Pronounced hyperkeratosis results in slower freezing since cornified epidermis is a good insulator for heat and cold.

In applying liquid nitrogen to a small lesion, it is usually necessary to interrupt contact with the applicator. If this is not done, freezing proceeds rapidly to a greater depth and particularly to a greater width than is needed. Thus the treatment usually consists of touching the growth intermittently often enough and long enough to confine the freezing to the area desired for as long a period as required. Often if there are two or three lesions in close proximity, they can be treated coincidentally by alternately transferring the applicator saturated with the liquid nitrogen from one to the other. The desired depth and width of freezing can be determined by the appearance of the lesion, since the area actually frozen is white and easily visible.

The time required to freeze a lesion adequately varies with its depth and thickness, its size and character. To one familiar with this method, accurate timing may not be necessary. However, results are apt to be more uniformly successful if a lesion to be treated is first "sized up" and then the determined period of freezing timed. The time is measured as the period during which the liquid nitrogen is actually being applied. It usually takes fully as long and sometimes longer for the frozen lesion to

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thaw out after the application has been discontinued. No hidebound timing schedule can be outlined. In treating hemangiomas, a period of ten seconds or less may be enough, and more intense freezing may predispose to ulceration. However, in most lesions a period of from 15 to 60 seconds will be used. For small superficial lesions on thin delicate skin such as that on the face and the dorsum of the fingers and hands, and of the forearms in children, 15 or 20 seconds may suffice. Juvenile plane warts and early keratoses may be treated in this manner. Lesions on the tougher thicker skin of most adults, especially on the palmar or plantar surface, require the longer periods. Common warts on the back of the hands, for example, may require 30 seconds. For most lesions on the palmar surface, from 45 to 60 seconds is necessary. If the lesion is cornified or imbedded as are warts on the grasping surfaces, 60 to 90 seconds may be required. Plantar warts are not often treated with liquid nitrogen because their depth makes adequate freezing difficult even with prolonged application.

The freezing produces stinging pain which is usually not considered severe. This persists to lesser degree for two or three hours and then disappears.

Following treatment with liquid nitrogen, redness and swelling develop within a few minutes. Blistering is delayed for several hours and reaches a peak on the second or third day. In treating lesions which are to be destroyed, the desired reaction is one in which a blister is produced in a narrow zone about and beneath the lesion, separating it from the normal surrounding tissue.

The patient should be told to return in 24 to 48 hours after treatment to see if satisfactory reaction has developed. If it has not, the lesion may be retreated at that time.

The author does not usually open and drain the blisters or remove the tops of them. Rather, the blister top is left in place. This makes the after-care simpler since secondary infection rarely occurs and dressings are not required. The blister dries and the top separates and exfoliates spontaneously within about three weeks. Patients are asked to return as soon as this has taken place. It is usually possible then to tell whether or not the lesion has been treated successfully. If a wart has not completely disappeared, it will be smaller, shallower and devoid of horny covering. A second treatment applied then is much more likely to complete the removal than if retreatment is delayed. In an occasional case the blister continues to spread beyond the area frozen. Apparently pressure of the vesical fluid causes this enlargement. It seems to occur most commonly in lesions localized over joints or pressure points. When this occurs the vesicle top should be removed promptly and a sterile dressing applied.

In treating conditions involving larger areas, such as contact dermatitis, scarring in acne vulgaris and patches of lichenified eczema, a somewhat different technique is usually used. A larger applicator is needed. Several of the smaller common 6-inch applicator sticks may be combined, or a sturdier stick can be made by wrapping cotton about the end of a suitable length of quarter-inch doweling. This larger applicator is then dipped into the liquid nitrogen and applied either in a slow rolling or sliding manner. In treating the conditions mentioned, the reaction desired is less intense, and severe blistering is usually avoided. Slowly sliding such an applicator over the skin with moderate pressure may suffice to produce sharp delayed erythema followed by exfoliation. Such mild reactions may be of some value in the treatment of alopecia areata.

The low temperature of the liquid nitrogen causes a rapid condensation of atmospheric moisture on the cotton applicator. Thus, if several lesions are being treated or if several patients are treated in rapid succession, the applicator may become coated with ice. This interferes with its saturation with the liquid nitrogen. Likewise ice collects slowly about the opening of the thermos jug and may float on top of the liquid nitrogen. When all the liquid gas has evaporated, the ice will thaw and collect in the bottom of the thermos as water. Such icing is minimized in the commercial containers made expressly for transportation and storage of these gases by the small size of the opening. The container should be emptied and dried before it is refilled.

Liquid nitrogen has been of greatest use in the treatment of warts of the common and juvenile plane types, and it is frequently used in the treatment of superficial keratoses, both seborrheic and senile types. Although with pressure and increased length of freezing, liquid nitrogen can be made to be quite destructive, the author does not use it where appreciable thickening or infiltration of the base of a keratosis is present. Electrodesiccation is preferred for such lesions. In the author's opinion, freezing with liquid nitrogen is the best method for the removal of permanent freckles commonly seen on the exposed skin in older people, if such removal is desired.

The use of liquid nitrogen in hemangiomas is best confined to the more superficial hypertrophic vascular nevi. Solid carbon dioxide is more often used for such lesions, especially if the tumor is elevated or thickened more than a few millimeters. Liquid nitrogen may be satisfactorily used in treating small senile angiomas and the lesions of nevus araneus. In the latter, electrolysis or a fine electrodesiccating spark may be preferable if the central punctum and individual radiating vessels stand out clearly.

Superficial leukoplakia may be satisfactorily treated with liquid nitrogen. If the lesion is in the oral cavity, the patient should be instructed to hold his breath, since the intense cold fogs the moist atmosphere and obscures vision. Keloids, particularly if small, may be improved by freezing with liquid nitrogen, and the lesions of folliculitis cheloidalis have been improved greatly by freezing. The margins of individual pitted scars may be smoothed by this treatment and diffuse pitted scar-

TABLE 1.—*Results of Treatment of Common Warts with Liquid Nitrogen*†

154 patients; follow-up period 4 to 15 months

	No. of Patients	Per Cent	No. of Warts	Per Cent
Cures	97	63	243*	57
One treatment	60	39	111*	26
Two treatments	24	16	58	14
Three treatments	13	8	74	17
Failures	40	26	110*	25
One treatment	18	12	43*	10
Two treatments	11	7	22	5
Three treatments	3	2	13	3
More than three treatments	8	5	32	7
Partial cures (some warts disappeared, others did not)	17	11	77*	18
Cures				
One treatment			36*	8
Two treatments			10	2
Three treatments			2	....
More than three treatments			....	....
Failures				
One treatment			17*	4
Two treatments			6	1
Three treatments			5	1
More than three treatments			1	....

† Cowell Memorial Hospital, Student Health Service, University of California.

* Number of warts not accurate; represents least number in each category; if all records were complete, totals would be greater.

ring such as follows acne vulgaris may be conveniently treated by less intense repeated freezings with liquid nitrogen.

Acute contact dermatitis such as that produced by exposure to poison oak or ivy has long been treated by freezing with liquid gases. At the Student Health Service clinic at the University of California, this method has been in use for at least 25 years. Although it is difficult to evaluate such treatment by comparison with untreated controls, it is the author's impression that it is of value particularly when applied early to small lesions. When the dermatitis is widespread, use of the method is not practical. Similarly, isolated lesions of stubbornly resistant lichenified eczema and hypertrophic lichen planus have been treated by this method, with perhaps some improvement and relief of itching.

In granuloma annulare and stubborn discoid lupus erythematosus, in which a sharp inflammatory reaction extending to some depth is desired but in which destruction of tissue is to be avoided, solid carbon dioxide may be preferable.

Pyogenic granulomas have been successfully treated with liquid nitrogen, but the results of electrodesiccation and curettage are more uniformly successful.

Liquid nitrogen is of sufficient value in the treatment of warts and keratoses alone to justify keeping it at hand. It is easily and relatively quickly applied and lends itself to use on patients with multiple lesions. The pain involved is not great. After-care is simple. No dressing is used unless the vesicle is broken. Complicating secondary infection is rare and residual scarring is minimal. With superficial lesions no appreciable scar is to be expected. In deeper lesions mild to moderate depigmentation and perhaps slight atrophy result. It produces less scarring than other methods. Atrophy and depigmentation are noticeable only when repeated intense freezing is used, as for example in deep, resistant periungual warts. None of a number of physicians who have used this for years in the clinic and in offices has ever seen a keloid result from its use, even when deep and intense reactions are produced.

In an attempt to evaluate the use of liquid nitrogen in the treatment of warts at the clinic at the University of California, Berkeley, 154 patients, all of whom had common warts, were followed for from four to fifteen months. The results are summarized in Table 1.

While these results leave much to be desired, they are sufficiently good to justify the use of this method at least in selected cases of warts until some more specific treatment becomes available.

In order to visualize what takes place when liquid nitrogen is applied to the skin, two areas of normal skin approximately 0.75 cm. in diameter on the abdomen of an adult white male were frozen with light pressure for 45 seconds. One of these was excised after 30 hours and the second after eight days. Under the microscope a section of the 30-hour specimen showed a vesicle which had raised the epidermis cleanly from the dermis at the dermo-epidermal junction. The dermis was edematous, especially in its upper portion, and showed slight basophilic degeneration. There was a mild infiltrate of inflammatory cells scattered throughout the dermis. The majority of the cells were polymorphonuclears, but some round cells were also present. The section of the eight-day specimen showed the degenerated remains of the old epidermis which constituted the roof of the vesicle. A newly regenerated epidermis, two or three or more cells thick, was already present. Edema and cellular infiltrate were less pronounced than in the 30-hour specimen.

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Ruptured Cervical Intervertebral Discs

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SUMMARY

Intractable pain in the neck and upper extremity is frequently radicular in character and mechanical in origin. Rupture of a cervical intervertebral disc is the most common cause.

Diagnosis and localization are more difficult in the cervical than in the lumbar region. Pantopaque myelogram should be considered only as a mean of localization. Operation should be preceded by a thorough trial of conservative treatment.

RUPTURED intervertebral discs in the cervical region present considerably different problems in diagnosis and surgical management than do similar lesions in the lumbar area. The factors which add to the complexity of the problem in the cervical region are largely anatomical in nature. The vertebral column in the cervical region contains not only the nerve roots but also the spinal cord. Consequently, the symptoms may result from involvement of the nerve root or of the spinal cord or of any combination of these two structures. Other factors are the greater mobility of the cervical spine and the more localized cutaneous representation of the individual nerve roots in the neck than in the lumbar region. Motor disability, when present, is more pronounced in view of the greater specialization of individual muscles in the upper extremity.

Another anatomical factor which increases the complexity of diagnosis in the upper extremity is the formation from the cervical nerve roots of the brachial plexus along the path of which are many important structures, such as the scalenus anticus muscle, the subclavian artery, the clavicle and the pectoralis major muscle, as well as the first rib. All of these structures are theoretically capable of producing irritation to the brachial plexus with clinical signs which may be difficult to distinguish from those of a radicular lesion.

SYMPTOMS

Theoretically, rupture of an intervertebral disc can occur at any level in the cervical spine. However, as in the lumbar region, there are certain sites of predilection. The most frequent sites of rupture are between the fifth and sixth and between the sixth and seventh cervical vertebrae. Since there are seven cervical vertebrae and eight cervical nerve roots, the root which takes exit between the fifth and sixth cervical vertebrae is the sixth cervical root. That between the sixth and seventh cervical vertebrae is designated as the seventh cervical root. Compression of either root produces a clinical picture which permits accurate neurological localization.

Mechanical lesions involving the nerve root produce motor and sensory findings of radicular character, in contradistinction to the motor and sensory findings produced by a lesion affecting a peripheral nerve.

Irritation of the sixth cervical root produces symptoms in the distribution of both the radial and median nerves corresponding to those fibers in the peripheral nerve which take their origin from this nerve root alone. When the sixth cervical root is irritated by mechanical pressure, the sensory findings are limited to numbness and paresthesias involving the thumb, first and second fingers. The pain accompanying such a lesion, however, may vary widely in distribution. It generally affects the area between the vertebral margin of the scapula and the vertebral column, the region over the anterior pectoralis major muscle, in the precordial region, as well as the neck, shoulder, upper arm and along the radial aspect of the forearm. The pain generally does not extend into the fingers. Weakness is usually confined to the triceps muscle.

When the seventh cervical root is irritated, the sensory findings of numbness and paresthesias involve chiefly the third and fourth fingers. The motor loss involves not only the triceps muscle but also the extensors of the wrist and fingers. The pain associated with seventh root compression is more often limited to the shoulder, arm and forearm.

The onset of symptoms varies greatly in individual patients. Frequently there is a history of recurrent attacks of stiffness of the neck associated with pain and muscle spasm, but no evidence of radiation into the arm or forearm. Months or even years later, the sudden onset of severe radicular pain involving the arm may be precipitated by some physical effort such as lifting, coughing or sneezing. Symptoms occur in attacks of short duration, usually followed by a period of more or less complete freedom. Attacks tend to become more frequent in occurrence with extension of pain into the neck, shoulder and, later, the arm and forearm. The attacks recur on the same side with symptoms appearing in identical areas with each attack. Frequently the patient complains only of pain and numbness, being unaware of the presence of any muscular weakness. During an acute attack, any muscular effort involving the neck or arm may be extremely painful. Likewise, in most

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radicular lesions, coughing, sneezing or straining may aggravate the pain. Night pain, particularly between two and four o'clock in the morning, is common.

DIFFERENTIAL DIAGNOSIS

A ruptured intervertebral disc in the cervical region may present difficulty in diagnosis because of the greater number of important structures which must be considered as etiological factors. Lesions which must be considered in the differential diagnosis are cervical arthritis, scalenus anticus syndrome, cervical rib, old fracture of the clavicle and, if the pain is on the left side, coronary heart disease.

Symptoms produced by a ruptured intervertebral disc are often attributed to the presence of radiologically visible arthritis of the cervical spine. It is true that arthritis may produce radicular symptoms, but usually these are not confined to one upper extremity. A compression syndrome involving one nerve root should not be attributed to primary cervical arthritis without thorough neurological investigation.

The scalenus anticus syndrome is without doubt a clinical entity, but it does not exist anatomically nearly as often as it is diagnosed clinically. The primary feature of this syndrome is compression of the subclavian artery, with pain a secondary factor. Without objective evidence of vascular disturbance, the diagnosis should be made with caution. Obliteration of the radial pulse should be readily demonstrable and limited to the side of the clinical symptoms. Section of the scalenus anticus muscle for pain alone, particularly when limited to the radial aspect of the hand, seldom results in relief of symptoms.

The presence of a cervical rib on the side of the pain and paresthesias may make the differential diagnosis difficult. It is helpful to recall that the site of the mechanical irritation caused by a cervical rib involves the brachial plexus directly; hence the distribution of pain and paresthesias is more widespread than can result from compression of a single nerve root. If, after adequate investigation, doubt still exists concerning the essential lesion, it is better clinical judgment to resect the scalenus anticus muscle first, since this procedure is less formidable than cervical hemilaminectomy.

Poorly united fractures of the clavicle are liable to produce excess callus formation, particularly on the under surface. Such lesions have been observed to produce very localized areas of pain and paresthesia in the upper extremity. Old fractures of the first rib with callus formation likewise may produce a point of mechanical irritation to the brachial plexus. Wide resection of that portion of the clavicle or first rib results in complete relief of symptoms.

Suspected coronary heart disease may lead to confusion in diagnosis when the radicular symptoms are limited to the left side. This is particularly true when the sixth nerve root is involved, since pain may be limited to the anterior pectoral region on the left with radiation into the left upper arm. Patients having recurrent attacks of severe pain, without other features of angina and with repeatedly normal electrocardiograms, should be considered as having a ruptured intervertebral disc. The presence of muscular weakness in the triceps or extensors of the wrist and fingers should be of definite aid in establishing a correct diagnosis.

Lesions more nearly in the midline affect primarily the spinal cord and must be differentiated from spinal cord tumor, multiple sclerosis, primary lateral sclerosis and syringomyelia.

The most consistent diagnostic feature of spinal cord tumor, early in its course of development, is the presence of symptoms and signs gradual in onset and progressive in character. A history of trauma is usually lacking, as well as recurrent acute attacks of pain and muscle spasm in the neck. Night pain is a characteristic symptom of spinal cord tumor. Frequently pain awakens the patient from a sound sleep and is relieved if the patient gets out of bed and walks about the room. Pyramidal and spinothalamic tract signs may be present in either type of lesion, but the history of steady progression is seldom present with ruptured intervertebral disc.

Primary lateral sclerosis should offer little difficulty in diagnosis because the pyramidal tracts are the only portion of the spinal cord affected. Exaggerated deep tendon reflexes, increased muscle tone and positive Babinski signs without sensory impairment are diagnostic.

Multiple sclerosis is characterized by remissions and exacerbations of clinical signs and symptoms. The cardinal features of this syndrome are nystagmus, pronounced incoordination and pyramidal tract signs. The history of old retrobulbar neuritis, appearing even years before the onset of other symptoms, may afford a clue to the proper diagnosis.

Primary cavitation of the spinal cord should offer little difficulty in differential diagnosis because of the long history, the muscular atrophy, as well as the presence of a well-defined zone of disassociated anesthesia corresponding to the area of involvement of the spinal cord.

The diagnosis of ruptured intervertebral disc should be made by clinical means. No special laboratory procedures can take the place of careful history taking and neurological examination. Special diagnostic procedures such as x-rays, electromyogram, lumbar puncture and Pantopaque® myelography should be employed to eliminate the etiological possibilities and to localize the actual site of the lesion.

Roentgenograms of the cervical spine should be taken routinely. They should include three-quarter views of the spine and a projection through the mouth as well as the routine anteroposterior and lateral views. X-ray findings associated with ruptured intervertebral disc include the loss of the usual cervical curve, a point of localized narrowing of the intervertebral disc, and hypertrophic changes of the adjacent vertebrae. Frequently, these localized hypertrophic changes are considered as primary

cervical arthritis, but in all probability they represent a secondary reaction of the adjacent vertebrae to an abnormal mechanical factor at the level of the ruptured intervertebral disc. In normal circumstances the intervertebral disc has a very high water content, and consequently any motions of the cervical spine produce a distribution of force which follows a hydrostatic principle. Secondary to degeneration of the intervertebral disc and subsequent rupture, there results a decrease in the water content of the disc. Motion of the cervical spine then produces a stress and strain on the adjacent vertebrae which follows a mechanical rather than a hydrostatic principle. In such circumstances, forward motion of the cervical spine results in far greater force being placed upon the anterior margin of the vertebrae, and over a period of time there result hypertrophic changes, particularly along the anterior margins of the adjacent vertebrae, which account for the localized changes so frequently seen in association with a rupture of one of the cervical intervertebral discs. It would seem most unlikely to find a far advanced arthritic process limited to two adjacent vertebral bodies without some evidence of involvement of the remaining cervical spine.

The electromyogram has recently proved to be of great value in the differential diagnosis, particularly of those lesions which affect the motor component of the nerve root. A careful electromyographic examination will reveal evidence of lower motor neuron disease as demonstrated by the presence of fasciculation in the individual muscles supplied by the motor component of the involved nerve root. This excellent adjunct to neurological diagnosis has not been fully investigated. However, the authors believe that the presence of positive electromyographic evidence affords a reliable means of localization.

The value of lumbar puncture and careful cerebrospinal fluid investigation cannot be overemphasized. The procedure is done with the patient in the horizontal position. The needle should be introduced carefully to prevent blood contaminating the spinal fluid. Determination of the initial pressure and the response to jugular compression are carried out as a routine procedure. A complete examination of the spinal fluid obtained should be done without delay. The most important spinal fluid examination in the diagnosis of ruptured intervertebral disc is the determination of the total protein. An elevation of the total protein generally signifies a lesion producing nerve root or direct spinal cord irritation.

Myelography has proven to be of great value, but it should be considered as a method for accurate localization of the lesion and not employed to replace clinical diagnostic procedures. The accepted medium used at present is Pantopaque. All too often myelography has been used as the first method of investigation rather than the last. Cervical myelography is a difficult procedure and should not be attempted by those unfamiliar with fluoroscopic technique.

TREATMENT

The proper care of individuals with intractable pain in the upper extremity requires careful clinical judgment. It must be remembered that not every pain in the shoulder and arm results from ruptured intervertebral disc. Other types of neuritis occur which are not of a mechanical nature. Careful clinical investigation should be made to exclude sites of focal infection. Referred pain from a ligamentous lesion adjacent to the spinal vertebral column may simulate a radicular syndrome. When not to operate is as important in this as in any other surgical problem. It would seem safe to state that no patient should be operated upon during the first attack of pain, no matter how severe, without first having conservative treatment. This should consist of heat, physical therapy and traction. Oftentimes even skeletal traction is necessary in order to obtain sufficient pull without discomfort to the patient. It is probable that over 90 per cent of individuals will obtain complete relief in the first or even subsequent attacks by such conservative procedures.

The indications for operation are failure to obtain benefit by conservative means, the appearance of pronounced increase in the positive objective neurological findings, or the development of spinal cord signs.

The actual surgical removal of the ruptured intervertebral disc is not difficult. It is purely a mechanical problem consisting of the location and removal of the offending fragment, which is generally located far laterally beneath the nerve root at the level of the involved intervertebral disc. Removal is best accomplished under general intratracheal anesthesia with the patient in a sitting position. Both the midline incision and partial hemilaminectomy should be adequate to allow proper exposure. Thus, removal of the fragment may be accomplished without damage to the nerve root or the adjacent spinal cord. The approach is extradural. The dura itself is not opened except in rare instances, because the presence of spinal fluid serves as a hydrostatic buffer which protects the spinal cord.

The lesion may appears as a bulging of the posterior longitudinal ligament or as a complete rupture through the ligament into the extradural space. Frequently an area of bony reaction is found about the margin of the herniated portion of the disc material, and it is generally advisable to remove the area of bony reaction as well as the cartilaginous material. After removal, the wound is closed in layers without drainage.

No special postoperative care is necessary, and patients are allowed out of bed on the first or second day.

Complete relief of symptoms can be anticipated if adequate care is exercised in the selection of patients for operation.

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Treatment of Miliary and Meningeal Tuberculosis in Infants and Children

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SUMMARY

Streptomycin and combined streptomycin-promizole treatment of miliary and meningeal tuberculosis in infants and children at the Los Angeles Children's Hospital has resulted in clear-cut arrests in seven patients, two of whom had meningitis. A much longer period of observation will be necessary before these patients may be considered cured. These results are incomparably better than the universally fatal outcome of both diseases in a large and unselected group of untreated cases which has been studied. Promizole, and possibly also para-aminosalicylic acid, should be given concurrently with streptomycin. As they are relatively harmless drugs, they should be given to ambulatory patients for a long period of time after arrest of the disease to decrease the likelihood of recurrence. If necessary, streptomycin may be given for longer than 90 days, or in second courses, since combined chemotherapy apparently delays the appearance of streptomycin-resistant strains of tubercle bacilli. The current pessimism with which many pediatricians view miliary and meningeal tuberculosis is unwarranted. Optimism will be rewarded with many more recoveries in the future.

MILIARY tuberculosis and tuberculous meningitis have for a long time been the most dread forms of a much-feared disease, and particularly for the pediatrician. The majority of deaths from tuberculosis among infants and children are as a result of disseminated miliary tuberculosis or of tuberculous involvement of the brain and meninges. Some 70 per cent of all cases and deaths from tuberculous meningitis occur in the pediatric age group.[13] Since the advent of the sulfonamides and penicillin, most acute infectious diseases of infants and children have become readily curable, thus spotlighting these two infections entailing so high a mortality rate.

Acute disseminated miliary tuberculosis is, without treatment, an almost universally fatal disease in children, although a few spontaneous recoveries have been reported. Occasionally a child is seen in whom roentgenograms demonstrate multiple miliary calcifications in the lungs, liver and spleen, presumably the result of a previous widespread hematogenous dissemination of tubercle bacilli, which the body has managed to heal without outside assistance. For all practical purposes true caseous tuberculous meningitis is universally fatal in the absence of specific chemotherapy. No spontaneous recovery from classical tuberculous meningitis has been reported. Thus, prior to the introduction of streptomycin, a pediatrician confronted with a child with miliary or meningeal tuberculosis could do little more than offer symptomatic care. Lincoln[8] has described a new syndrome, serous tuberculous meningitis, to be discussed later in this presentation, from which spontaneous recoveries have been reported.

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STREPTOMYCIN

Streptomycin has considerably changed the picture in the treatment of tuberculosis, and for the two forms of the disease under discussion it has proved a bright ray of hope. A number of arrests of miliary tuberculosis in all age groups have been reported, and there are a few well documented apparent recoveries from tuberculous meningitis. Many clinicians have observed pronounced improvement in children and adults with tuberculous meningitis treated with streptomycin, only to have their hopes dashed when the disease recurred a few months after health apparently had been regained and the treatment stopped. One of the best studies of a large group of streptomycin-treated patients is that of Bunn,[2] who reported on the first 100 consecutive cases of miliary and meningeal tuberculosis in adults treated in 52 Veterans Administration hospitals during 1946 and early 1947. These patients were all given streptomycin in large dosage, both intramuscularly and intrathecally, for an average of 120 days each. They were followed up to June 1948, or from 13 to 26 months from the beginning of treatment. Of 22 patients having miliary tuberculosis alone, nine had died and 13 were living. Of 43 patients who had tuberculous meningitis alone, 34 had died and nine were alive. And of 35 patients who had both miliary tuberculosis and tuberculous meningitis, 33 had died and only two remained alive. Thus at the end of one to two years, only 24 per cent of all the patients

were alive, and of those having meningitis only 14 per cent were alive. In a series of 105 cases of tuberculous meningitis studied by the Medical Research Council in hospitals in England and Scotland,[11] at the end of a minimum of four months' observation, only 12 per cent of a group of 33 patients under the age of three were alive and doing well, while 36 per cent of a group of 72 children and adults over the age of three were making good progress.

There are apparently two good reasons why the initial dramatic improvement observed in many patients with miliary and meningeal tuberculosis who are treated with streptomycin is not maintained. The first is the development of streptomycin resistance by the infecting tubercle bacilli after a variable period of treatment. Several groups of investigators[1, 4, 15] have observed in adult pulmonary tuberculosis, where tubercle bacilli may be readily recovered at intervals during streptomycin therapy, that at the end of three months of treatment 40 to 50 per cent of the strains recovered showed significant streptomycin resistance, and at the end of four months of treatment 70 to 80 per cent of the strains recovered have become resistant to the drug. The second reason for relapse after initial favorable response to streptomycin, especially in the case of tuberculous meningitis, is the persistence of a caseous tuberculous focus which does not heal and in which viable tubercle bacilli remain beyond the reach of streptomycin and ever ready to break out anew into the blood stream or the subarachnoid space. Rich and McCordock[12] in 1933 demonstrated pathologically that tuberculous meningitis is not due to a direct hematogenous seeding of the meninges, but to a preexistent caseous focus, usually a tuberculoma, which discharges tubercle bacilli directly into the subarachnoid space.

In the last two years, particularly since it has been demonstrated that streptomycin is not the final answer in the treatment of tuberculosis, various new efforts have been made in the treatment of miliary and meningeal tuberculosis. Lincoln[9, 10] at Bellevue Hospital has introduced the use of promizole, one of the sulfone compounds which has some tuberculostatic activity. She was able to achieve arrests in three cases of miliary tuberculosis using promizole alone, and to gain encouraging preliminary results in tuberculous meningitis in children, using a combination of streptomycin and promizole. In Italy the combination of streptomycin and sulfone is being used.[3, 5] At the Mayo Clinic[6] a combination of streptomycin, promin and para-aminosalicylic acid (PAS) is being used in the treatment of certain cases of pulmonary tuberculosis. PAS has a strong in vitro bacteriostatic action against virulent tubercle bacilli, and has been shown to exert a beneficial effect on experimental tuberculosis.[16] Finally, Waksman,[14] the discoverer of streptomycin, has recently described a new antibiotic, neomycin, which has pronounced antituberculous action and which, although not yet available for clinical use, offers considerable hope for the future.

NATURAL HISTORY OF UNTREATED DISEASE

Experience with miliary tuberculosis and tuberculous meningitis at the Los Angeles Children's Hospital bears out many of the conclusions briefly described in preceding paragraphs, but the experience in the last two years has been sufficiently encouraging to be worth reporting. A review of data on the two diseases before the advent of specific chemotherapy provides a useful basis for comparison against results obtained with chemotherapy. During the 15 years 1934 to 1948 inclusive, 146 patients with miliary and meningeal tuberculosis were admitted to the hospital and given only symptomatic treatment. Twenty-one patients had miliary tuberculosis, 58 had tuberculous meningitis, and 84 had both diseases. Of the 146 patients, all died of the disease. For the group the average duration of life from the onset of symptoms was 20 days for those with meningitis, and 40 days for those having miliary tuberculosis alone.

PATHOLOGY

Autopsies were done on 80 infants and children who died of tuberculous meningitis. In 27 of these patients (34 per cent) one or more tuberculomata were demonstrable in the brain, these caseous foci being pathologically older than the tuberculous involvement of the leptomeninges. In some cases the brain was not sectioned, and in others no careful search for caseous foci was made, so that it is probable that actually more than 34 per cent of these patients had tuberculomata antedating meningitis. A second significant finding was that in 17 of the 80 autopsied patients with meningitis, there was no evidence of miliary tuberculosis elsewhere in the body. Other patients with advanced tuberculous meningitis pathologically, showed only a minimal, early hematogenous seeding in the lungs, liver and spleen, suggesting that the miliary spread as well as the meningitis derived from the older caseous intracranial focus. These data support the theory of Rich and McCordock[12] that tuberculous meningitis is the result not of a direct seeding of the meninges from the blood stream, but of actual rupture of an expanding intracranial caseous focus into the subarachnoid space, or of migration of tubercle bacilli to the meninges from an activated intracerebral tuberculoma via the Virchow-Robin lymph spaces.

UNSUCCESSFULLY TREATED PATIENTS

Since 1946, 22 infants and children with bacteriologically proven miliary and meningeal tuberculosis have been treated with streptomycin at Los Angeles Children's Hospital. Twelve of these patients were given promizole in addition. In five of the 22 cases, treatment was not started until the disease was in a terminal stage. All of these five patients died promptly, but each was moribund on admission, and each received less than seven days of treatment.

Six additional patients were treated unsuccessfully. Of these, two who had both miliary and meningeal tuberculosis died after one and two months,

respectively, of streptomycin treatment. Two patients died during the first recurrences of tuberculous meningitis, occurring five and ten months, respectively, after original attacks which responded favorably to streptomycin. One of these patients was given promizole in addition to streptomycin. A fifth unsuccessfully treated patient died of far-advanced caseating pulmonary tuberculosis, seven months after successful arrest of miliary and meningeal tuberculosis by combined streptomycin-promizole therapy. The remaining unsuccessfully treated patient is still alive, but seems destined to die. He is currently in the second recurrence, or third attack, of meningitis. In the first two attacks streptomycin alone was given and the meningitis cleared completely. In the present attack, both streptomycin and promizole are being given, but no significant improvement has been noted.

SUCCESSFULLY TREATED PATIENTS

Seven infants and children were successfully treated, five of them with streptomycin alone, and two with the addition of promizole. Five of these patients had miliary tuberculosis without meningitis. Each is now in good health. They have been observed respectively, 32, 28, 25, 12, and seven months since the onset of miliary tuberculosis. Two infants and children who had combined miliary and meningeal tuberculosis have had arrest of the disease. One of the two was given streptomycin, and one combined streptomycin and promizole. Both are living, mentally normal, and free of meningeal involvement 24 and seven months, respectively, since the beginning of treatment. One is in good health, and one still has tuberculous osteomyelitis in the right foot which existed before the meningitis. In addition to the seven patients classed as successfully treated, four children with meningitis are currently being treated in the hospital, and although the period of observation has been short, two seem to have a good chance of recovering.

PLAN OF TREATMENT

The plan of treatment followed in 1946 and 1947 consisted in an average streptomycin dosage of 1 gm. daily, given in three-hourly intramuscular injections, for an average period of 90 days. Those patients with meningitis were also given intrathecal streptomycin, 50 to 100 mg. daily or every other day for the first one to two months of treatment. More recently the plan of treatment has consisted in intramuscular streptomycin given only once every 12 to 24 hours, in a total daily dosage of from 0.25 to 0.50 gm., for a period of 90 days. Twelve patients with meningitis have been given intrathecal streptomycin in addition, in a dosage of 10 to 20 mg. every two to four days; and four patients with meningitis have been given no intrathecal streptomycin. One of the two patients who were successfully treated for tuberculous meningitis received no intrathecal streptomycin. Promizole has been given orally in a total daily dosage varying from 1 to 8 gm., depending on body weight, with the dosage gradually increased until a serum promizole level of 2 to 3 mg. per 100 cc. is obtained. The plan calls for continued administration of promizole for a period of two years following discontinuance of streptomycin.

TOXICITY

The toxic effects of treatment in the seven successfully treated patients, and in the four unsuccessfully treated patients who survived for some months, have been chiefly the loss of vestibular function produced by streptomycin. The earlier patients, who received 1 gm. daily for 90 days, all developed persistent loss of vestibular function as demonstrated by the caloric test, but this has been well compensated, and the children walk well now and show no disturbance of balance. Two successfully treated recent patients, given 0.5 and 0.25 gm. daily, have not had disturbance of vestibular function. One child who was treated in another hospital for the first two attacks of tuberculous meningitis and who was given large amounts of streptomycin both intramuscularly and intrathecally for a total of 140 days, now has severe ataxia and is unable to stand. A second child, who received large doses of streptomycin intrathecally for one month at another hospital, became both blind and deaf six months before death; it is difficult to say whether these effects should be ascribed to streptomycin or to severe meningitis. A third infant who was given 1 gm. of streptomycin intramuscularly daily for three months, as well as 50 mg. intrathecally daily for five weeks, became completely deaf after arrest of tuberculous meningitis. In those patients given streptomycin intrathecally it was noticed that anorexia and vomiting were often increased; and in one patient who was given streptomycin intrathecally, signs of temporary transverse myelitis repeatedly appeared near the site of administration soon after injection.

There is considerable disagreement as to the advisability of using streptomycin intrathecally in the treatment of tuberculous meningitis, since it is known that the drug does appear in the spinal fluid after intramuscular injection, and in larger amounts where pathological inflammation of the meninges exists. Levinson[7] has recently reported eight successful arrests of tuberculous meningitis among 19 children treated without intrathecal use of streptomycin. On the other hand, the British clinicians coordinated by the Medical Research Council[11] found a significantly higher number of patients made good progress when the drug was given intrathecally. In experience so far at the Los Angeles Children's Hospital, good arrest of caseous tuberculous meningitis was obtained in one case in which the drug was not given intrathecally, and there was evidence of increased toxic reaction when the intrathecal route was used.

No significant toxic effects of promizole have been noted thus far in patients at Children's Hospital. Some patients had considerable vomiting while receiving promizole, but this is also a common symptom of tuberculous meningitis. Pronounced

erythematous rash developed in one child, but it later disappeared without discontinuance of promizole. All patients frequently passed red urine. The red color was found to be due to the presence in the urine of a metabolic breakdown product of promizole of unknown structure. The chronic toxic effects of promizole administration described by Lincoln,[9] namely thyroid enlargement with reduction in colloid, and breast hypertrophy in females, have not been observed at Children's Hospital, perhaps because at the time of this report none of the patients had received promizole for longer than seven months. Serum iodine determinations on several patients after three to four months of promizole therapy have all been within normal range.

STREPTOMYCIN SENSITIVITY OF TUBERCLE BACILLI

Attempts have been made to study the streptomycin sensitivity of tubercle bacilli isolated from the more recently treated patients. In every case the organisms isolated at the beginning of therapy proved highly sensitive to streptomycin, growth in vitro having been suppressed by 0.5 micrograms of streptomycin per cubic centimeter of culture medium. In only two cases has it proved possible to isolate strains from patients after long periods of treatment. Strains isolated from the spinal fluid of one child after 143, 187, and 212 days of streptomycin therapy were, surprisingly, still sensitive in vitro to 0.5 micrograms per cubic centimeter. Tubercle bacilli isolated from the spinal fluid of a second child after 101 days of streptomycin treatment were also sensitive to 0.5 micrograms per cubic centimeter. This failure of tubercle bacilli to develop the expected resistance to streptomycin after long periods of treatment is particularly interesting in view of the recent finding by Hinshaw and his coworkers[6] that in patients treated for pulmonary tuberculosis with a combination of streptomycin, promin and PAS, the tubercle bacilli developed resistance to streptomycin very slowly. Thus these adjuvant tuberculostatic drugs not only add to the beneficial effect of streptomycin, but appear to prevent the overgrowth of naturally occurring or mutant streptomycin-resistant organisms.

REASONS FOR THERAPEUTIC FAILURE

Little has been learned so far in the present series as to the reasons for therapeutic failure in those patients in whom treatment was started before the terminal stage of the disease. At autopsy of one child who died after one month's intrathecal and intramuscular streptomycin treatment four small tuberculomata in the brain were noted; one of them opened directly into the subarachnoid space and might therefore have caused a particularly heavy infection of the meninges. At autopsy of an infant who died of recurrence of tuberculous meningitis six months after return to good health following intramuscular and intrathecal streptomycin treatment of miliary tuberculosis with meningitis, multiple tuberculomata were noted in the substance of the brain. These lesions had blocked the aqueduct and had led to hydrocephalus. A third infant in whom miliary and meningeal tuberculosis were successfully arrested by combined streptomycin and promizole treatment, eventually died of extensive cavitating tuberculosis of one lung. However, it is suspected that in certain cases of both miliary and meningeal tuberculosis, even the best of therapy is foredoomed simply because tuberculous lesions of such extent that they cannot conceivably be healed already exist in the brain or elsewhere in the body.

SEROUS TUBERCULOUS MENINGITIS

It should be added that one of the two patients in whom meningitis has been successfully arrested probably had a syndrome termed by Lincoln[8] "serous tuberculous meningitis." This relatively benign form of the disease is thought to be due to meningeal irritation secondary to perifocal reaction around a lesion in the brain associated with an extension of tuberculosis elsewhere in the body. The signs and symptoms of serous and of true caseous tuberculous meningitis are the same. Features that distinguish the former from the latter are (1) absence of chemical changes in the spinal fluid, (2) failure (usually) to recover tubercle bacilli from the spinal fluid, and (3) the fact that patients with serous meningitis may recover without specific chemotherapy. In the one case of serous tuberculous meningitis in the present series, pronounced pleocytosis in the spinal fluid developed during the course of intramuscular streptomycin treatment of miliary tuberculosis, but there were no signs or symptoms of meningitis. The spinal fluid protein, sugar and chloride levels remained normal, and tubercle bacilli did not grow on cultures of the spinal fluid.

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The Neurological Program of the Veterans Administration

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SUMMARY

The reorganization of the medical department of the Veterans Administration has given considerable impetus to neurology, a part of the division of psychiatry and neurology. The neurologic service of the V. A. is the largest in the world today, and is constantly increasing. This service is made available to veterans through hospitals and regional offices within the designated area, which are branch administrative offices under the central office.

A residency training program for specialization is under the direction of a deans' committee in every large medical center. This committee, which is formed from the faculties of medical schools, also approves the visiting medical staffs of hospitals. The neurologic program consists of a number of special activities, which include residency training for certification, neurologic diagnosis, rehabilitation of patients with chronic illness, electroencephalography, epilepsy, aphasia and research. The paraplegia program is now a separate service, but is also participated in by the neurologist. Both the neurologist and the psychiatrist are interested in the patient with organic psychosis, and the neurologist also works in close relationship with the neurosurgeon.

There is need for neurologists in the V. A., which offers attractive opportunities in clinical practice and in research, as well as inducements of advancement and adequate financial returns.

PRIOR to the adoption of the present medical program of the Veterans Administration the specialty of neurology in the United States was at a distressingly low ebb, save in several well established and recognized neurological centers. This alarming situation has recently been discussed in a number of papers. The author, in the presidential address before the American Neurological Association in 1946, stressed the importance of the basic neurological sciences to medicine, and to psychiatry in particular; in the same year addresses followed by Percival Bailey, and by George Wilson and Charles Rupp. The reactivation of neurology was made an important issue by Henry Riley in his presidential address before the American Neurological Association in 1947, and also by George Wilson as president in 1948.

It is here pertinent to discuss the reasons for this situation. Neurologists have always felt secure in what they believed to be an uncontested recognition of the importance of the most highly organized system of the human body, the nervous system, to those specialties identified with this system. Therapy has frequently been neglected by the neurologist, who has favored diagnosis and research. Quite the opposite situation prevails in the case of the neurosurgeon, who stresses treatment, and for this reason, neurologic cases are often directly referred to the neurosurgeon, by-passing the neurologist. Neurologists have not participated in movements of national interest, some of which are essentially of neurological nature—poliomyelitis, for example. They have not availed themselves of opportunities to obtain federal and other research grants by representation on important committees. Conservatism often connotes lack of aggression. Neurological services and cases are frequently taken over by internists, who are fearful of partitioning of their own specialty. Economic considerations facing the student aspiring to neurological specialization are often deterrent in the selection of this specialty. Today, most neurologists include psychiatry in their practice.

Important as are the foregoing factors in the dilemma of the neurologist, no single factor, in the author's opinion, is as important as the lack of support by many medical schools; and according to a recent survey this is especially so in the western United States. Such lack of support is evidenced by the absence of a properly organized neurological service, despite the proportionate representation of neurology in curricular hours as compared with other specialties, and the professorial rank of teachers. Approval of a residency training program in neurology has consequently been delayed by the Council on Medical Education and Hospitals of the American Medical Association. In 1948, only two residents in neurology were provided for in approved civilian hospitals in California. The attitude of the medical schools is reflected in the attitude of the medical profession in general, and is not to be wondered at, when recently one of the younger physicians asked me in all sincerity, "Is there any longer such a specialty as medical neurology?"

In 1946 the reorganization of the medical department of the Veterans Administration began to assume definite shape under Generals Omar N. Bradley, Administrator of Veterans Affairs, and Paul R. Hawley, chief medical director. Guided by the best interests of the disabled veteran, two changes were made: One, decentralization; the other, the formation of deans' committees.

For facility of administration, 13 subdivisions,

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known as branch offices, were formed, each provided with a deputy administrator and a medical director. A recent major administrative reorganization abolished the branch offices and, for the purpose of medical supervision, has established five area offices as extensions of central office. Headquarters for these five area offices are located in San Francisco; Fort Snelling, Minnesota; St. Louis, Missouri; Atlanta, Georgia; and Boston, Mass.

Central Office: The central office is located in Washington, D. C. Dr. Paul B. Magnuson is the departmental head of medicine and surgery. The medical specialties are represented by divisions, such as the division of psychiatry and neurology, the division of medicine, the division of surgery, and others. Subdivisions of these specialties are known as sections. Dr. Harvey J. Tompkins is head of the division of psychiatry and neurology, and Dr. Pearce Bailey is head of the section of neurology. An over-all advisory committee assists Dr. Tompkins in professional and administrative problems. The chief medical director has several assistant medical directors, one of whom is Dr. E. H. Cushing, assistant medical director for research and education.

Area Offices: The San Francisco area office serves as a center for the supervision of the medical activities of Veterans Administration installations located in the states of California, Oregon, Washington, Idaho, Utah, Nevada and Arizona, and the territories of Hawaii and Alaska. The San Francisco area office is staffed with one full-time neuropsychiatrist, Dr. Lyle L. Woodfin, whose position title is chief of neuropsychiatry section. He supervises the psychiatric and neurological activities of the area. Area consultants in both psychiatry and neurology, appointed from the central office, contribute to the program by assisting in the selection of medical personnel, by offering advisory consultation, and by serving on special committees named by the chief medical director in the central office. Dr. Karl M. Bowman is area consultant in psychiatry, and is also a member of the San Francisco deans' committee and the subcommittee for neuropsychiatry. Veterans Administration neuropsychiatric activities reach the veteran through regional offices and hospitals.

Regional Offices: Regional offices are located in large centers of population in each area. Here the veterans are examined for pension and compensation purposes and receive treatment on an outpatient basis. Hospitalization is available either in neuropsychiatric hospitals or in neuropsychiatric services in general medical and surgical hospitals.

Deans' Committees: Members of medical school faculties constitute the deans' committees. They are empowered to formulate the educational and training programs in Veterans Administration hospitals under their auspices, to recruit specialists, and to appoint attending and consulting physicians to the various services. Residency and staff appointments are subject to their approval. In this way the Veterans Administration hospitals in the deans' committee program become identified with medical school methods of education and research, and hold to similar standards. Hospitals in remote areas are not now included, but ultimately may be. In these "nonteaching hospitals" a program of instruction has been set up, in which area consultants participate.

This seemingly involved scheme of organization operates quite smoothly in actual practice, considering the large number of invalided veterans and associated personnel. Approximately 60 per cent of all patients in veterans' hospitals fall into the neuropsychiatric classification, and a third of these are neurological. The neurological service of the Veterans Administration is the largest in the world today. Moreover, the patient load is constantly increasing. As an example, the peak patient load of World War I is only expected this year (1949). The number of epileptic patients in the next ten years is expected to reach 50,000. At present there are about 15,000 traumatic epileptics of record.

Relationship of Neurology to Psychiatry, Neurosurgery: In the Veterans Administration neurology is concerned largely with the patient with an organic lesion of the nervous system, whereas the psychiatrist is responsible for the diagnosis and treatment of the patient with psychoneurosis or functional psychosis. Both are interested in the patient with organic psychosis and both contribute freely in any case in which a combination of the talents of psychiatrist and neurologist are needed. At the hospital level psychiatry and neurology are represented by a chief of service qualified in both neurology and psychiatry and preferably certified in each. Other neuropsychiatrists may function under the supervision of the chief of service, depending upon the size of the service. Neurosurgery is a section under the surgical service. There is a close association between neurology and neurosurgery. A neurological and neurosurgical unit has been planned for the Veterans Administration neuropsychiatric hospital at Los Angeles. The accepted procedure is for neurosurgery to clear through medical neurology, save in emergencies or by special arrangement. Dr. Glen Spurling is the head of the national neurosurgical program and this service is represented in the San Francisco area by Dr. David L. Reeves.

The Veterans Administration programs in neurology consist of a number of special activities, which operate for the most part in large diagnostic and treatment centers.

The Residency Training Program: As of April 1949, there were 14 residency training programs in neurology in operation. Two of these are in California, one at the Veterans Hospital at Van Nuys, the other at Fort Miley, San Francisco. Approved residents are assigned to duty on neurological wards, they attend medical school courses, and by rotation in other services are grounded in the different neurological disciplines. Veterans are given credit for neurological experience gained in the last war; nonveteran residents are recruited from recent medical school graduates. Applications are processed through the chief of service in a training center hospital, to

be eventually reviewed by the deans' committee. After the formal requirements of education demanded by certification boards have been fulfilled, the additional requirement of practice for certification may be met wholly or in part by becoming a staff member of a Veterans Administration hospital. There were 49 neurological residents in Veterans Administration hospitals as of February 1949. Ample financial assistance is given the resident qualified for residency training.

The Rehabilitation Program: Retraining and activation of persons suffering from chronic nervous disorders has been particularly studied at the Veterans Administration Hospital, Minneapolis, and results there have been so successful that a training center has been established at that station. In this area a sub-training center has been set up in the Veterans Administration Hospital at Oakland. The psychiatrist, the physical therapist, the psychologist, and the social service worker participate in teamwork with the neurologist to form a well-rounded program. Many helpless, bedridden veterans have been improved to the extent that they have been able to help themselves, leave the hospital, and return to their homes.

The Electroencephalography Program: The national EEG program is under the direction of Dr. Frederic A. Gibbs, who gives regular courses of instruction at the University of Illinois School of Medicine, Chicago. Any neurologist connected with the Veterans Administration neurological program may make application to attend this course. There is a repository of EEG records at the Hines Veterans Administration Hospital, Chicago, for future reference and research.

The Epilepsy Program: Dr. William G. Lennox of Boston directs the national program of the study of epilepsy. The headquarters of this activity is the Cushing Veterans Hospital at Framingham, Massachusetts. This is a center for all activities concerned with the care and study of the epileptic patient. Dr. Earl Walker of Baltimore heads the traumatic epilepsy program.

The Aphasic Program: This national program is headed by Dr. J. M. Nielsen of Los Angeles. His speech clinic is located at the Birmingham Veterans Administration Hospital at Van Nuys. This program has achieved recognition from the laity as well as the medical profession. Other aphasic centers are located at Framingham and at Minneapolis.

The Research Program: The Veterans Administration neurologist is eligible for federal research grants. Applications are made though Veterans Administration hospital clinics or medical schools associated with deans' committees. Approved projects are then reviewed by a subcommittee of the National Research Council, which reports back to the Veterans Administration and renders an opinion as to the value of the proposed research from the professional standpoint. The research in epilepsy was one of the first established. There are approximately five others under way.

The Paraplegic Program: This program was set up originally under the neurosurgery section of the surgical service but was later made a service within itself. Neurologists, urologists and other specialists participate in this program. There is a large service at the Birmingham Veterans Administration Hospital, Van Nuys, where the number of patients is constantly over 200. Dr. Ernest Bors, a urologist, conducts this service.

There is great need for trained neurologists, especially those qualified to head services, in Veterans Administration hospitals. The central office is constantly requested to provide neurologists, and must often reply that none is available. This shortage applies likewise to attending and consulting neurologists and has been a hindrance to the progress of the neurological program. The medical profession is, however, becoming aware of the exceptional opportunities for education, practice, and research in neurology through the Veterans Administration, and an encouraging interest is shown in inquiries and applications. The opportunity for a follow-up study in neurological cases is unparalleled. Compensation is comparable to that prevailing in other similar federal services and to that in the better-compensated medical school appointments. Grades commence with junior rating and run successively through associate, full, intermediate, and senior to chief, which is the highest rating either in the central or the area office. Advancement is limited only by limitation of ability. Compensation increases with length of service. Those certified in specialties are given 25 per cent over base pay. Pension and retirement provisions are similar to those enjoyed by comparable government services.

The value and need of neurologists in the Veterans Administration have proven an active stimulus to neurology in general and have called attention to the necessity of both setting up acceptable standards for teaching neurology in medical schools and disseminating information as to the true meaning of neurology as related to other specialties. Activities along such lines have been shown by the recent creation of the American Academy of Neurology, now with a membership of over 700, and appointments of public relations committees of the two national neurological societies. It is the earnest wish of those interested in neurology, representing the basic neurological sciences, to aid in every way the related specialties with which this branch of medicine comes into daily contact. This applies particularly to psychiatry.

In closing, a quotation of a great physician and organizer, General Paul R. Hawley, former head of the medical department of the Veterans Administration, may not be amiss. It is taken from an address before the Philadelphia Neurological Society, delivered on October 24, 1947. General Hawley said, "Regardless of any trends, it appears indisputable that the future of psychiatry will depend in large degree upon discoveries emanating from neuropathology and neurophysiology."

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Coccidioidomycosis of the Meninges

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SUMMARY

In a review of 53 cases of coccidioidal disease, 50 of which resulted in death, some symptoms were noted to be so common as to facilitate diagnosis. Laboratory studies of spinal fluid gave helpful information. Particularly noteworthy with regard to roentgenologic studies was the fact that in no case in which there was pulmonary cavity formation due to coccidioidomycosis did coccidioidal meningitis develop.

IN the last approximately 50 years coccidioidomycosis due to coccidioides immitis has been an important public health and medical problem in Central California, particularly in the southern end of the San Joaquin Valley.

In any discussion of coccidioidal granuloma, coccidioidomycosis of the meninges is an important phase.

Smith[2] and co-workers in a review of the literature stated that this mycotic infection has been noted to be endemic in western Texas along the Mexican border, in southern New Mexico, in southern and central Arizona, in southwest Utah and in the southern tip of Nevada. In California the disease is endemic in the southern San Joaquin Valley with irregular distribution up as far north as Modesto, Merced and Tracy, and in eastern Ventura and Santa Barbara counties. In southern California some cases have been reported in San Bernardino, Riverside and San Diego counties.

Because there is so much traveling by the general public, physicians will be on the alert for this disease not only in western United States, but also in other areas of the country.

Now that coccidioidal granuloma has been added to the list of reportable diseases, it is to be expected that a continual study of this disease will have additional significance to health officers in California.

All of the areas in which coccidioidomycosis is endemic are arid or semi-arid. The common finding is that the onset of the majority of the cases of coccidioidal meningitis within the boundaries of Kern County has been in the period May through November. However, the severity and frequency of dust storms occurring even in the so-called wet season implies that coccidioidal granuloma, with or without meningitis as a complication, may occur at any time during the year.

Physicians working in the Kern County Hospital and Health Department have estimated unofficially that some 67 cases diagnosed as coccidioidomycosis of the meninges have occurred in Kern County in the 13 years since 1936. Since reporting has not been complete and errors have occurred in the differential diagnosis of coccidioidomycosis of the meninges in this group of cases, this presentation will consider 53 selected cases. The diagnosis in each instance was confirmed by clinical, laboratory, biopsy and, in many instances, autopsy evidence.

Of the first 147 known and reported cases of coccidioidal granuloma that occurred in Kern County from 1901 to 1936, 67 were fatal. Of the 67 patients who died, only nine were stated to have had coccidioidal meningitis. It is interesting to note that three of the first four Kern County patients reported to have died of the disease were reported to have had coccidioidal meningitis.*

In a study by Kirshbaum† of 53 fatal cases of coccidioidal granuloma in Kern County, it was noted that 29 of the 53 patients also had coccidioidomycosis of the meninges. Kirshbaum felt that the lymphatic system acts as a barrier preventing dissemination to the meninges; upon a hematogenesis basis, fatal meningitis might have developed in even a greater proportion of cases.

Generally the incidence of coccidioidomycosis of the meninges is about twice as great in males as it is in females. In the age group 20 to 40 years there is even greater disparity; in this age span almost thrice as many men as women are affected. There is also a relatively higher incidence in Indians, Filipinos, Negroes, and Chinese than in white persons. Although the non-white group constitutes only about 8 per cent of the population in Kern County, almost 50 per cent of the total cases of coccidioidal meningitis have occurred among them.

Gifford,[1] in a study of coccidioidomycosis in Kern County which she reported in 1939, noted not only this disparity in incidence with regard to race and sex, but also that the death rate was considerably greater among males than females. She also called attention to the fact that in recent years more

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* From a study made by M. A. Gifford, M.D., for the Kern County Health Department.

† J. Kirshbaum, M.D., who then was pathologist at Kern General Hospital.

of the non-granulomatous, non-fatal type of coccidioidal disease had been reported and that more of these cases were reported in women than in men.

In the present study of 53 cases of coccidioidal meningitis few changes were noted with regard to factors of incidence relative to age, race, sex, occupation and area of habitation. Once more endemic foci have been shown in rural areas about Bakersfield, Delano, Shafter, Arvin, Wasco, and the Greenfield and Lakebottom areas. Fifty per cent of these cases of coccidioidomycosis of the meninges occurred in persons employed in the agricultural industry. More than 80 per cent of the patients who died were engaged in work in which dust could well have been an occupational hazard.

In the series here under consideration, the diagnosis was established by various means—by history, physical findings, laboratory studies, biopsy, and autopsy. A high index of clinical suspicion was developed as a result of the frequently common findings in the typical cases of coccidioidal meningitis.

Headache, often severe, persistent and resistant to routine treatment, was one of the common symptoms in the older patients; there were only a few who did not have frontal and occipital headache. (In many cases this symptom was relieved by timely aspiration of spinal fluid.)

Signs of meningeal irritation were common. Severe stiffness of the neck and spasms of the neck muscles were noted in most cases. Symptoms related to the eyes consisted of photophobia, blurring of vision and diplopia. Chest and abdominal pain was less common, although when pleurisy or pneumonitis (as confirmed by x-ray) persisted, the chest pain was more severe.

Subjective mental aberrations frequently were noted in association with headache, neck stiffness, and chest pain. Loss of memory, disorientation, comatose stages, paraphasia and other mental changes were observed, particularly in the terminal stages of meningitis.

Usually there was steady fever of several degrees. In a few cases there was no febrile stage. In terminal phases and with onset of complications the fever was explosive and very high. In some cases 106° to 107° F. was observed before death.

In many of the cases the early symptoms were insidious and presented difficulty in the problem of differential diagnosis. Among the diseases that most often had to be considered in differentiation were tuberculous and influenzal meningitis, purulent bacterial disease of the meninges, poliomyelitis, arthropod-borne encephalitis, post-viral encephalitis (measles, mumps, etc.), and prodromal stages of typhoid fever, dysentery diseases and pneumonia.

In a previous study carried out by Smith, Gifford and others, it was found that positive reaction to a skin test occurred usually in nine to 11 days after onset of illness with coccidioidomycosis. However, in cases of coccidioidomycosis of the meninges, since the disease was a part of a chronic disseminated pattern, it was noted that many of the patients were anergic. In only three such cases was there positive reaction, and in all three it occurred during the terminal month of illness. Although in most of the cases both mantoux and coccidioidin skin tests were done as early as possible after coccidioidomycosis was suspected, by and large the skin tests were of little value in making the final diagnosis. In two cases of coccidioidal meningitis, tuberculous and coccidioidal infection were concurrent; one of the patients had tuberculous meningitis as well as coccidioidal meningitis.

Two other very common observations in these cases were:

1. In many instances absence of evidence of lesions in x-ray films of the chest was important in helping to exclude tuberculosis. In only a few cases was there active mycotic pulmonary disease, as determined by x-ray or necropsy, at the time of death.

2. Although the primary portal of entry was pulmonary, there were no instances of cough that was more than transitory and non-productive in nature.

Results of laboratory studies were valuable aids in diagnosis. Examination of the spinal fluid was most helpful. In only one instance was the spinal fluid cell count normal; and in only one instance was the count more than 3,000 cells for each cubic mm. In about 90 per cent of the cases, cells in the spinal fluid numbered between 200 and 1,300. The spinal fluid was drawn soon after the onset of meningeal involvement. In the few instances in which the spinal fluid pressure was measured, it was above normal; commonly, 270 to 300 mm. of water was noted as the initial pressure. The pressure was reduced upon the removal of 15 to 30 cc. of fluid. In the average case the fluid was slightly cloudy to clear; in some instances it was xanthochromic or light green and of gelatinous consistency. In two cases in which clear spinal fluid was incubated for 24 to 48 hours a fungoid growth (later identified as coccidioides immitis) was obtained. In some cases a very heavy pellicle formed in the specimen of fluid within 24 hours, but in only one such instance was coccidioides immitis isolated. In seven cases the diagnosis was established by growth on cultures of gastric washings. Examination of direct smears and results of cultures on Sabaroud's media and other media frequently disclosed no coccidioides.

In tests on the spinal fluid, the colloidal gold curve was significant. In about 90 per cent of the cases there were colorimetric changes to the left of the color zone similar to that seen in paresis.

In only a few cases did coccidioidomycosis develop in guinea pigs that were inoculated with spinal fluid from the patients. Total protein content of the spinal fluid was abnormally high in more than 75 per cent of cases. In the spinal fluid of some patients the total protein was 150 mg. or more per 100 cc. The differential cell count of fluid taken in the early stages of illness showed up to 100 per cent polymorphonuclear cells in some instances. Frequently there was a preponderance of polymorpho-

nuclear cells in early specimens, with a gradual decrease later and a corresponding increase in lymphocytes. Almost complete spinal fluid block was observed clinically in two cases, and in one of the two, postmortem examinations proved this clinical assumption to have been correct. The number of cells in the spinal fluid did not have any direct relation to the severity of the illness.

Results of urinalysis were not of definite diagnostic help. Blood cell counts, which were done routinely in many instances, showed little diagnostic value. Leukocytes frequently numbered between 10,000 and 14,000, with polymorphonuclear cells relatively increased in number. In a few cases eosinophilia was noted in differential count of leukocytes. Secondary anemia was noted in a few instances.

The sedimentation rate of blood taken from the more acutely ill patients was accelerated, and this information was of some value in determining prognosis. The greatest value gleaned from determination of sedimentation rate, however, lay in the help it gave toward completion of diagnosis and, in some cases, in excluding other than the correct diagnosis.

Serology tests done on serial specimens of blood and spinal fluid sent to Stanford University School of Medicine were helpful. In serial dilution, precipitin and complement fixation antibodies were observed in many cases. Complement fixation antibodies were last to appear, and the persistence of antibodies, especially in high dilution, sounded a serious prognostic note. With few exceptions, heavy antibody formation was associated with clinical severity of the illness.

X-ray findings of disease in the chest and other areas, particularly bone, were helpful in those cases in which the disease was widely disseminated. Furthermore, roentgenologic evidence of pulmonary cavities due to coccidioidomycosis was profoundly important, for in no case of meningitis due to coccidioides was there pulmonary cavity formation. When pulmonary cavity formation existed in coccidioidal infection, the course of illness was benign.

In the fatal cases of coccidioidal meningitis in the present series, the duration of the illness varied from six weeks to about two years. Of the 53 patients, 15 died within three months after onset of acute illness, 23 within 12 months; seven lived more than one year and two lived almost two years. In three cases the duration of illness was not known, and three patients known to have coccidioidal meningitis are still living.

AUTOPSY

In 35 of the 53 cases the presence of coccidioidomycosis of the meninges was confirmed by postmortem findings. In each instance most of the pathologic changes noted were at the base of the brain and in the meninges. It was noted generally that the meninges were thickened and edematous and the vessels hyperemic. In many of the cases there was a definite exudate over much of the total brain area. The exudate, in a number of cases, surrounded the nerve roots. In those cases in which the disease had been of the more chronic nature, very frequently the convolutions of the brain were thickened and the meninges were thin. On examination of sections it was noted that the ventricles in most instances were dilated and filled with clear or straw-colored spinal fluid.

Epithelioid cells were frequently noted in microscopic studies of exudate from the base of the brain, the pons and the medulla. Heavy infiltrations of plasma cells, round cells and eosinophilic leukocytes were a common observation. There were frequently scattered giant cells. In some instances the coccidioides spherules were conspicuous, in others not. Areas of necrosis and numerous elements of fibrocellular proliferation were observed in some of the sectioned material.

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Pathology and the Pathologist in the Cancer Program

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SUMMARY

Cancer as one of the most important human diseases does not present as formidable a problem as infectious disease did a century ago. The diversified cancer program, combining voluntary and governmental agencies in support of research, education and coordinated teamwork in the clinical care of the patient, presents a varied although unified approach to the problem that has never before been available for the study of any single human disease. Pathology, with its applied methods from the basic sciences, has a singular role in the scientific aspect of the cancer program. Representing a new specialty in medicine and embodying an inquiring approach to the study of human disease, pathology has a leading role to play. The pathologist, assuming the new role of "pathologist-physician" brings to the clinical care of the cancer patient the most precise methods of cancer diagnosis. The "pathologist-physician" should be a pivotal member of the "clinical team" in the immediate diagnosis, care and treatment of the cancer patient.

HUMAN life is one of the most precious things in the world and the responsibility for its care is largely in the hands of the medical profession. Much of the future progress, destiny, and happiness of the human race is, to a great extent, dependent upon the progress made by medical science in the knowledge and understanding of human diseases. For centuries man has stood in awe of human illness and cloaked his existence with all manner of superstition to compensate for his inadequacy in the comprehension of the basic knowledge of the factors that control his existence on this earth. The history of the 20th century will have many important events to be chronicled by historians, let us say, in the year 2500 A.D. We have already seen in the first half of this century such noteworthy things as two world wars (each contributing, we hope, to the advancement of individual freedoms and rights) and, of course, the explosion of the atomic bomb. These events loom large and overwhelmingly significant to us at the moment, and a majority of opinion now would regard the atomic bomb as the most notorious accomplishment of man. It is entirely possible, however, that the historian of the year 2500, having the background and perspective of several hundred years when reviewing the events of the 20th century, will pass by all of these and list as the most important human achievement of the century the discovery of the causes of certain important diseases, as this knowledge may have proved helpful in the prevention of premature death and the sparing of human pain and misery.

What has provided the impetus for this advance in the knowledge of human disease that may rival the atomic bomb for posterity's acclaim of human accomplishment, and what have been the methods used to attain such noteworthy advancements? To break through the veil of superstition that attended such basic biologic events in the life of man as death and birth, that was so prevalent in the middle ages, has taken one basic quality of human thought working slowly over the centuries. This is the inquiring human mind that has asked repeatedly the one-word question, "Why?" The most successful method has been the joining of human minds and social agencies in pitched battle against individual diseases or groups of diseases. The result has been smashing victories on many fronts. One hundred years ago, 80 out of every hundred persons died of some infectious disease before the age of 40, and now, 80 out of every hundred live beyond the age of 40.[9]

It is the purpose of this communication to discuss the important role of one branch of medical science epitomizing the inquiring attitude of medicine and its qualified medical specialist in a planned attack on one of the now most prevalent and serious of human diseases. That disease is cancer; the specialty is pathology; the specialist is the pathologist; and the planned attack is the organized effort of scientific and governmental agencies participating in the cancer program.

THE DISEASE (CANCER)

Cancer today is the second leading cause of death in the United States.[12] It is, however, a much less formidable problem than any of the important infectious diseases were a century ago, before the establishment of the concept of their cause from an infectious agent transmitted from one person to another. Cancer, for example, does not have the striking power against man of such uncontrolled infectious diseases as cholera, dysentery, plague and yellow fever that have so frequently altered the destiny of nations and whole races of people by deci-

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mating armies and civilian populations. Although no common denominator for the causation of cancer has been established, important factors in the genesis of certain types of cancer are well recognized; viruses, x-rays, radium rays, ultraviolet rays, carcinogenic substances associated with certain occupations, intrinsic factors such as heredity, endocrine factors and fetal rests are only a few. Therapy for cancer now, although far from adequate, has much more to offer the patient than the accepted forms of therapy which were available to patients suffering from cholera, dysentery, plague and yellow fever in the past century. The general problem of cancer regarding its causation and therapy may be tersely stated as presenting a less formidable apparent barrier for a final solution than was presented by the infectious diseases in the last century. Today, we have much more fundamental knowledge upon which to base an attack.

THE SPECIALTY (PATHOLOGY)

Pathology is one of the newest specialties of medicine. It has claimed full-time practitioners of medicine working and recognized in the field for less than 40 years. Although pathology may be thought of as meaning "the study of disease," the science has come to have a much wider application to the practice of medicine, for which reason a fuller and more meaningful definition is applicable. Pathology has been best defined as "that branch of medicine which deals with the causes, the processes and the effects of disease."[3, 4]

The processes of disease involve the concepts of pathogenesis, and effects of disease are seen as clinical symptoms. In short, pathology is the science dealing with the questions concerning disease, asking, "where?", "why?", "how?", "what?", and "whether?" It has been this inquiring quality of thought and mind that has resulted in the major advances in the understanding, prevention and treatment of disease. The results of these attitudes and approaches in the understanding of human illness now being crystallized into the new specialty of pathology have largely paralleled the advances of scientific medical knowledge and the progress made in the diagnosis and treatment of disease.

THE SPECIALIST (PATHOLOGIST)

Pathology, as practiced today, was born in the first half of the 19th century when the "inquiring human mind" of practicing physicians was not content to treat patients symptomatically for such complaints as cough, weakness, and pallor. These physicians, the first practicing pathologists, asking themselves such questions as "why" did their patient die after years of cough, expectoration, and general body emaciation, were able to find some of the answers by performing postmortem examinations on the patient to see the structural alteration of the body causing the symptoms. This was the "period of clinical correlation" and it is highly significant that in this period some of the most classical descriptions of disease were written. Among these searchers were some of the most outstanding physicians of the day, such well-known investigators as Corvisart, Laennec, Louis, and Cruveilhier in France, and Hodgkin, Bright, Addison, Adams, Corrigan and Graves in England. In short, it was the age of the "physician-pathologist."

During this "period of clinical correlation" it became quickly apparent that the science of morbid anatomy (pathologic anatomy) in its relation to the causes, pathogenesis and clinical manifestation of disease was too large a field to be carried as a side activity for practicing physicians. It was at this time that the occasional man turned his entire medical practice to the performing of autopsies and the study of disease. In England, it was Robert Carswell; in Berlin, Rudolf Virchow; and in Vienna, Carl Rokitansky. With further development of the specialty of pathology there have been added besides straight, morbid anatomy for the purpose of clinical correlation, physiology, bacteriology, serology, and biochemistry, as these sciences may be applied to the practice of medicine. The pathologist, therefore, is a medical specialist who is integrating factual and definitive information obtained from his tests involving the basic sciences of medicine with clinical information in a more precise and scientific approach to the diagnosis of disease and the treatment and care of the patient than was ever possible before.

It would seem then that, if the pathologist is utilized in the fullest application of his specialty, the complete change from the "physician-pathologist" of the days of Bright, Addison and Laennec has been made and now he is the "pathologist-physician." The full significance and meaning of this is that now the physician-specialist, skilled and learned in the basic sciences of medicine, has returned to the practice of medicine as a fully qualified medical specialist.

THE CANCER PROGRAM (A COORDINATED ATTACK ON A DISEASE)

One of the best examples of a coordinated attack upon a human disease leading to the conquering of that disease was the work of the Yellow Fever Commission, which in 1900 was directed by the Surgeon General of the Unted States to visit Havana, Cuba, and investigate the cause of a large epidemic of yellow fever. The members of the Commission, Walter Reed, James Carroll, Jesse W. Lazear and Aristides Agromonte, were to solve one of the then most baffling of mysteries, when they discovered that the disease was caused by an ultramicroscopic filter-passing agent and was transmitted by a mosquito.[11] It was the joining of these minds in a local battle with a specific epidemic of the disease that produced the most significant single advance. The preparation of a prophylactic vaccine[10] followed, and it, together with the knowledge of the causative agent and vector, rendered this disease impotent as a major threat to human life in any civilized community.

Today, there are much greater forces mobilized and attacking the "disease cancer" than was possible

by the Surgeon General's Yellow Fever Commission in 1900, yet in less than a generation that disease was rendered impotent by frontal attack of well-conceived scientific procedure.

The impetus for the attack on cancer came from a voluntary, unofficial agency. The American Cancer Society, formerly known as the American Society for the Control of Cancer, was organized in 1913 by a group of physicians and other scientists who believed that the sum of the existing knowledge available for cancer control was not being utilized effectively because of ignorance on the part of the public and indifference on the part of the profession. Through their zeal and enthusiasm, the possibility of improving the cancer situation was dramatized to the point that federal, state, and local health agencies, medical schools and medical societies, as well as literally thousands of individuals, were enlisted in the fight. Funds raised by the society were matched by tax funds on a broad scale until the point has been reached where cancer research today is being pursued on a scale never previously contemplated. In addition to greatly stimulated programs of research, supported by governmental agencies, by private philanthropies, and local cancer groups, the American Cancer Society, from 1945 to 1948, has allotted no less than $9,679,000 for the research aspect of its program alone.[7]

In the field of education, in addition to increased enlightenment and interest on the part of the public, much is being done to coordinate and improve the teaching of cancer in medical schools. The long-range goal is the ultimate better care of the cancer patient resulting from an increased interest in the cancer problem on the part of the medical profession. In this regard it is particularly significant that in the medical literature the field has warranted the preparation of special indices.

There are now six publications for the indexing and/or abstracting of cancer literature. These are as follows:

1. Wolfe's Lebre von der Krebskrankheit (1907-1928).
2. Index to Literature of Experimental Cancer Research (1900-1935 Donner Foundation).
3. Index Analyticus Cancerologae (1927 to present).
4. Zeitschrift fur Krebsforschung (1903 to present).
5. Index to Current Periodical Literature on Neoplastic Disease (Louisiana State Division of the American Cancer Society, 1946 to present).
6. Cancer Current Literature (The American Cancer Society, 1947 to present).

That there is need for special indices and abstractings of articles on cancer is understandable, for there are over 15 medical journals devoted to cancer. No other single disease has such recognition in the medical literature.

The keynote of the cancer program is teamwork; teamwork between the official and voluntary agencies; teamwork between the medical profession and the agencies; teamwork between the patient and the patient's medical advisors; teamwork between the general practitioner and his specialist-consultants.[1, 6, 5, 3] Whether it be in the research laboratory, the university medical school or in the practice of hospital or private pathology, the pathologist, having the ubiquitous approach to scientific medical problems and being able to bring the most precise and accurate methods for the diagnosis of disease, is probably the most indispensable member of the cancer team. Pathology as a science has no methods of its own but applies the methods and procedures of the anatomist, the chemist, the physiologist and the microbiologist. When this fact is thoroughly appreciated and understood there is no limit to the application of the science to the study of a disease, and the contribution that can be made to the attack upon a single disease such as cancer is likewise unlimited.

THE PATHOLOGIST AND PATHOLOGY IN THE CARE OF THE CANCER PATIENT

The education program of the American Cancer Society, in all its manifestations, has emphasized that the patient should consult a physician for the most trivial symptoms, that cancer might be diagnosed in its incipient stages, to allow the maximal opportunity for the cure of the disease.[2] Obviously, this must be done even at the risk of creating undue apprehension in certain types of personality and at the risk of being accused of creating "cancerphobia." There is nothing truer than the Cancer Society's statement that "cancerphobia" is much easier to cure than metastatic carcinoma. We must be prepared for the occasional disturbed patient in order to attract the many curable patients now permitted to go their way undiagnosed. The plea is made to the general practitioner to be tolerant toward the patient whose trivial symptoms prove to be inconsequential.[6] We must also make a plea to the pathologist that he in turn be tolerant toward the general practitioner who persistently submits negative specimens, always remembering that the more curable the cancer the more difficult it is to diagnose and the more inconclusive the clinical evidence. The pathologist has been urged to make available to the practitioner of clinical medicine the most rapid and accurate methods of diagnosis of cancer. The pathologist, therefore, is an important member of a "clinical team." To bring the benefits of his specialty to their greatest usefulness in the care and treatment of the patient, the following suggestions are offered:

Tumor Clinics and Tumor Boards: Tumor clinics and boards serve their highest purpose and usefulness in that they provide opportunity for the correlated discussion of cancer cases by pathologist, radiologist, surgeon, internist and other specialists regarding the care and disposition of the cancer patient.[3] By the providing of jury opinion rather than judge decision in the care and disposition of cancer patients, the level of cancer therapy is immeasurably improved. The pathologist should be a leader in the tumor clinic[8] since by virtue of his

training and background in the basic sciences of medicine he brings an integrative and interpretive science to the "clinical team."

Tissue Diagnosis and Operating Room Consultation: This is a medical diagnostic service of phenomenal accuracy. The correct diagnosis of cancer is made in 98 per cent of cases when cancerous tissue is given to a qualified pathologist. This degree of accuracy in medical diagnosis is rarely equalled by other specialists in selected diseases. When in the operating room for consultation and frozen section diagnosis, the pathologist has unusual opportunity to bring the methodology of the science of pathology to its greatest fruition in the care of the cancer patient. He should allocate the maximal amount of his professional time for this kind of work since it provides golden opportunity for him to personally participate in the professional care of the patient with his professional colleagues. By this collaboration they will better appreciate the benefits to be gained by consultation with a medical specialist whose background and training are so fundamental and basic to the understanding of all medical problems. In this activity the pathologist is assuming the full role of "pathologist-physician"—a sharp contrast with the role of the first pathologists who were "physician-pathologists."

Obligation to the Medically Indigent Patient: The pathologist should serve the cancer patient in the same relationship as other physicians. In part-pay and indigent clinic practice the professional services of the pathologist should be given in accordance with the dictated customs of the other types of medical practice. Where his professional services are dispensed through non-professional channels, and particularly where he is in a master-servant relationship with lay authorities, the pathologist is hindered in giving his maximal value to the "cancer team," and the care of the cancer patient will consequently suffer.

IMPROVED TECHNIQUES AND DIAGNOSTIC TESTS IN THE DIAGNOSIS OF CANCER

The pathologist has the greatest responsibility of any specialist in the spectrum of medical practice to bring to the practicing profession the latest tests and methodology in the diagnosis of disease. Upon his choice and evaluation of methods used in his laboratory is dependent how rapidly advances in medical therapy reach the level of medical practice in the community. This is particularly true in the care of the cancer patient. Clinical laboratory diagnostic tests for cancer are constantly being suggested. The pathologist must be prepared to evaluate them, rejecting impractical and unsound procedure, yet rapidly instituting new methods if he feels they are desirable. In this function the pathologist largely controls the flow of scientific advances to the medical community. A stubborn refusal to investigate or adopt new methods of proven value cannot be justified by a true scientist.

Postgraduate Medical Education: By virtue of his intermediate position between the basic sciences of medicine and the clinical practice of medicine, the pathologist is in a preferred position to take the lead in educational activities. By being a leader in academic exercise in the medical community, he helps improve the general level of medical practice. In the final analysis every pathologist is a postgraduate medical educator, since in many instances he is the first contact the practicing physician has with new developments in the basic sciences of medicine. Great contribution can be made by the pathologist in the careful study of individual tumors and obtaining maximal information applicable to the individual case by participation in national and local tumor registries. If the tumor cases are properly recorded in a central agency for the collection of pathologic material and related clinical and laboratory data, then the collected material, besides providing opportunity for extended research regarding the life history of a given tumor, will provide material for individual research and a source of new information for tumor diagnoses.

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CASE REPORTS

- An Early Fatal Case of Infantile Toxoplasmosis in California
- Pancreatic Cysts Simulating Carcinoma of the Head of the Pancreas
- Anaphylactic Shock Following Intravenous Administration of Thiamine Chloride
- Allergic Parotitis

An Early Fatal Case of Infantile Toxoplasmosis In California

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IT is the purpose of this presentation to report a case of toxoplasmosis in an infant from California, believed to be the earliest on record in the United States.

Neonatal cases of toxoplasmosis are being reported with greater frequency. Nearly 40 such cases, proven either by isolation of the organism, by autopsy, or by both methods, have been reported to date.[3, 22] Clinically, toxoplasmosis in the newborn may manifest itself by enlargement of the head due to internal hydrocephalus, by chorioretinitis, and by signs of central nervous system irritation, such as convulsions, spasticity, reflex changes and hypothermia. On ventricular puncture, xanthochromic fluid of high protein content (grams per 100 cc.) is usually obtained. Occasionally, toxoplasma can be visibly demonstrated in such fluid. More successful, usually, are attempts at isolation of the organism by animal inoculation.

The protein and cell contents of the subarachnoid and spinal fluid are likewise increased. However, the protein levels are in the range of hundreds of milligrams per 100 cc., rather than the thousands of milligrams per 100 cc. as in the ventricular fluid. On radiological examination of the skull, intracerebral calcifications may be found. The latter are not as common, however, as chorioretinitis, which has been found in almost every neonatal case of toxoplasmosis, properly investigated.

Such are the signs and symptoms of most of the fatal cases described.[10] However, in a few cases of neonatal toxoplasmosis there have been manifestations of disease referable mainly to the extraneural viscera, such as icterus due to hepatitis, anemia and disturbance of growth.[7, 8, 16] Here again, chorioretinitis is usually present, and on autopsy a diffuse involvement of all of the viscera has been found.[7, 8] Nevertheless, many of the infants showing the latter symptom complex survive,[1, 4] and it is this symptom complex that is sometimes elicited in children with signs of chronic toxoplasmosis dating back to early infancy. Those infants showing signs and symptoms referable to the central nervous system are thought to have passed through a state of generalized visceral infection earlier, usually *in utero*, after acquiring the infection by the transplacental route.[3]

The causative organism, *Toxoplasma gondii*, is generally regarded to be a protozoan. Its name is derived from the Greek *toxon*, meaning a bow or arc, and referring to the lunate shape of the organism in the fresh state. The specific name *gondii* is derived from the name of the host in which the organism was first observed. This was the gondi (*Ctenodactylus gondi*, Pallas, 1778), a small North African rodent, which was used as a laboratory animal at the Institute Pasteur of Tunis and from which Nicolle and Manceaux first described toxoplasma in 1908 and 1909.[6] The organism is known only to reproduce by binary fission. Proliferative forms and so-called "pseudocysts" can be distinguished. The individual organisms usually appear spherical on sections. The early literature on toxoplasmosis has been reviewed by Sabin[10] and Weinman.[14]

Recently, one of the authors (J.K.F.) observed two and collected reports of two further cases of fatal neonatal toxoplasmosis. When these cases were presented and were discussed by the other author (H.C.N.) he recalled a similar case, which he had observed 26 years ago. Slides, paraffin-blocks, as well as the eyes of the baby had been preserved, so it was not difficult to make the diagnosis even at this late date. Fortunately, too, the baby's parents could be contacted and they were kind enough to submit to skin and serological tests for toxoplasmosis.

CASE REPORT

The patient was born prematurely at Adler's Sanitarium, San Francisco, in 1923. The head was enlarged, the fontanelles were bulging and the cranial sutures were separated. Right microphthalmia was noted. Surgical incision through the scalp overlying the anterior fontanelle revealed a tense bulging dura. The convolutions were not remarkable. Puncture of both ventricles revealed thick and yellow fluid. The temperature was unstable and the baby died at the age of five days.

Autopsy Findings. The body was that of an underdeveloped male infant without rigor mortis. The fontanelles and sutures of the cranial bones were widely open. Over the anterior fontanelle, a silver foil dressing closing a recent 3 cm. long incision was present. The right eye was distinctly smaller than the left. No significant gross findings were noted regarding the thoracic and abdominal viscera. On removal of the brain from the calvarium a large amount of yellowish fluid was found, containing several large accumulations of thick, tenacious material and small fat droplets. The cerebral hemispheres collapsed during removal. The brain was small and had a yellowish appearance, with a number of white, somewhat granular areas. There was microgyria of the right occipital lobe.

Microscopic sections of the heart showed several foci of subsiding myocarditis (Figure 1). Mild interstitial pneumonitis, slight hepatitis, splenitis and interstitial nephritis were present. In both eyes, foci of retinal degeneration, cellular infiltration and toxoplasma were observed (Figures 2 and 3). No brain material had been saved. A more detailed histopathological report will be made at a later date.

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Skin Tests and Serological Findings on the Parents. Twenty-five years after giving birth to the patient the mother proved to have positive reaction for Toxoplasma gondii by both the toxoplasmin skin test[2] and the toxoplasma neutralizing antibody test. The latter was positive as performed in the rabbit skin,[9] and an in vitro titer of 1:64 was obtained.[11] Reaction to skin test of the father, while negative at 40 hours, turned positive after 72 hours, and serum from the father likewise showed the presence of toxoplasma-neutralizing antibodies, both as demonstrated on the rabbit skin and in vitro (1:16). Neither of the parents' sera contained toxoplasma complement-fixing antibodies.[13]

COMMENT

Except for the first well-authenticated case reported by Jankû from Prague, Czechoslovakia, in 1923,[5] the case reported herein is the earliest case of toxoplasmosis diagnosed from pathological material. Of course, without knowledge of the pioneer work of Wolf and Cowen[15] and of Sabin[10] and others, the diagnosis would not have been made at the present time.

The advanced lesions of toxoplasmosis observed in the patient at the age of five days are evidence of antenatal inception of the disease. Certain evidence has been collected[2] to support the thesis that most mothers when transmitting the disease are in the acute stage of toxoplasmic infection, rather than in a stage of latent chronicity, which is thought to follow the acute stage. The mother in this case was stated to have had pernicious vomiting of pregnancy while carrying the patient. However, although she had similar symptoms during a subsequent pregnancy, she gave birth to a normal child.

It was of interest to note the positive reaction to skin tests and the presence of neutralizing antibodies in the blood

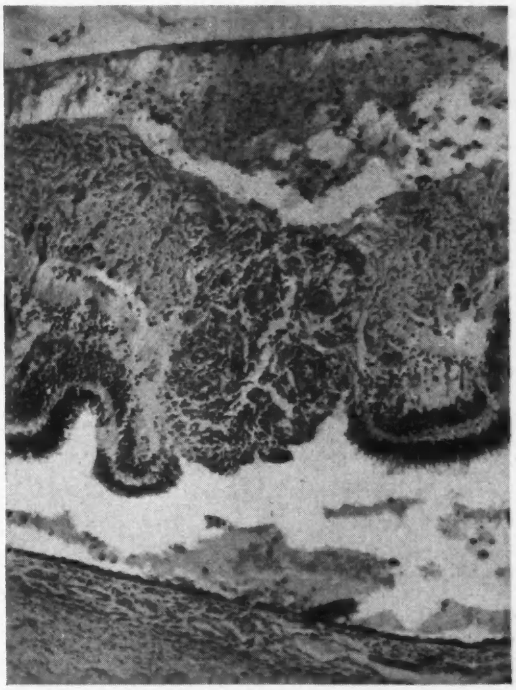

Figure 2.—Granulomatous retinitis (center) and slight choroiditis (below) with cellular exudate in vitreous (top) and between retina and choroid. Hematoxylin and eosin (x 80).

Figure 1.—Myocardial fibers showing necrosis, and infiltration by lymphocytes, plasma cells and larger mononuclear wandering cells; the endomysial fibroblasts are proliferating. Hematoxylin and eosin (x 325).

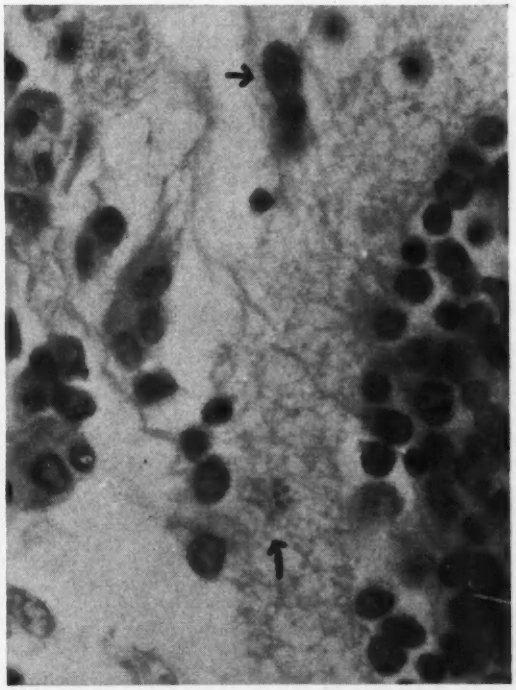

Figure 3.—Close-up of right center margin of area in Figure 2, showing two groups of toxoplasma in the outer fiber layer of the retina. Hematoxylin and eosin (x 845).

obtained from the parents. The date of the infection could not be determined. Such positive laboratory evidence of past toxoplasmic infection is frequently obtained in persons in an older age group.[2] A negative reaction to a toxoplasma complement-fixation test does not vitiate this observation, since such antibodies seem to disappear shortly after infection or the last contact with the antigen.[12, 3]

SUMMARY

A patient with congenital toxoplasmosis, fatal at five days of age, has been presented. The case is thought to be the earliest on record in the United States. The patient was observed at San Francisco, California, in 1923, and the diagnosis was made recently by finding toxoplasma and specific lesions in the pathologic material saved. Both parents, when examined in 1948, had positive reaction to the toxoplasmin skin test and the toxoplasma neutralizing antibody test.

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Pancreatic Cysts Simulating Carcinoma of the Head of the Pancreas

Report of Two Cases

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PANCREATICODUODENECTOMY as originally advocated in 1935 by Whipple[1] and his associates for the radical treatment of carcinoma of the papilla of Vater and the head of the pancreas has now become a recognized procedure. Although the early attempts to carry out this radical operation were associated with a high operative mortality, a better understanding of technique and of preoperative and postoperative care have made possible the radical resection of tumors involving the common bile duct, duodenum and head of the pancreas previously considered inoperable.

A number of modifications of the original two-stage operation as performed by Whipple have been made. With the use of vitamin K and blood transfusions to control hemorrhage and anemia, the trend is now toward a one-stage operation. Most surgeons now reimplant the cut end of the pancreas or pancreatic duct into the upper intestine to preserve the external pancreatic secretion, whereas Whipple considered this unnecessary and one of the main hazards of the procedure. Other modifications of the original procedure have to do mainly with the type and position of the anastomosis made to reestablish continuity and still prevent stenosis and troublesome regurgitation of bowel contents into the biliary tree.

With the technical problems solved, the main difficulty confronting the surgeon at present is one of early differential diagnosis. Unfortunately, a number of conditions involving both intra- and extrahepatic biliary passages give rise to similar clinical pictures and are extremely difficult to distinguish one from another. Too often the differential diagnosis is made late and surgical treatment undertaken when surgical extirpation is no longer feasible.

In general, the main consideration in diagnosis involves the differentiation between obstructive and non-obstructive jaundice, which unfortunately is occasionally impossible. In this connection, one must always keep in mind the frequent association of the two, particularly when obstructive jaundice itself has led to secondary degenerative changes in the liver.

Obstructive lesions of the extrahepatic biliary tree, both benign and malignant, although frequently easily distinguished one from the other, may produce clinical pictures so similar that positive differentiation cannot be made without exploratory laparotomy. For this reason it becomes imperative that the surgeon be prepared to recognize and undertake the surgical management of these lesions, regardless of their nature, as they present themselves in the operating room.

Unfortunately, gross and even microscopic examination at the time of operation will not always lead to a positive diagnosis. This is particularly true of obstructing lesions of the lower end of the common bile duct. Often a stone imbedded in the common duct near the ampulla of Vater, with inflammatory reaction about it, will simulate carcinoma. Carcinoma of the ampulla may cause stricture and obstruction without gross evidence of tumor. Inflammatory lesions of the pancreas often cause common duct obstruction and are grossly indistinguishable from carcinoma of the head of the pancreas, even with aid of frozen sections made at the time of operation.

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The purpose of this communication is to report two cases of benign cysts of the head of the pancreas. In one case the cyst was inflammatory in nature, and in the other apparently obstructive in origin. Intermittent obstruction of the common bile duct and jaundice were caused in both cases. The gross pathologic changes in each case at operation were indistinguishable from those of carcinoma of the head of the pancreas. Both of the patients were subjected to radical partial pancreaticoduodenectomy, one in a single-stage operation and the other in a two-stage procedure, under the mistaken diagnosis of carcinoma of the head of the pancreas. Both patients recovered uneventfully from the operation and are living and well.

CASE REPORTS

CASE 1: The patient, a male 40 years of age, had right subcostal pain radiating to the back, occasional nausea and vomiting and jaundice of eight weeks' duration.

On July 6, 1947, the patient started to have mid-epigastric pain about 4 or 5 p.m. For the next three days he was unable to retain food. There was occasional dull pain in the mid-epigastrium and to the right side, radiating to the back and around the right subcostal margin. At the initial examination the patient was icteric. The liver was slightly enlarged and just barely palpable below the costal margin on the right, and the spleen was not palpable. The icteric index was 55 units. Leukocytes numbered 12,000 with 71 per cent neutrophils and 22 per cent lymphocytes. Result of a test for urobilinogen in the urine was positive in 1:40 dilution. A Wassermann test was negative for syphilis. July 17, the icteric index was 12 units. The cholesterol content in the blood was 233 mg. per 100 cc. and the sugar content 105 mg. per 100 cc. The patient stated that during the first three weeks of hospitalization he had constant nausea and vomiting with pain on the right subcostal margin, radiating to the right side and to the back; and during that time the body weight had decreased 25 pounds. From June 9 to July 26 the temperature ranged between 99° and 100.5°F. daily. On July 29 there was another bout of pain. Leukocytes then numbered 16,800 with 69 per cent neutrophils and 9 per cent stab cells. The icteric index was 16 units, and the result of an indirect van den Bergh test was 6.3 mg. Gastric analysis showed 71 degrees of free acid, the fluid being positive for blood. X-ray studies of the gastrointestinal tract on July 27 revealed no deformities or intrinsic lesions of the stomach. It was felt that there was an extrinsic mass causing a defect of the greater curvature of the stomach. No abnormality was observed in a film of the chest. The gallbladder was visualized. A second gastrointestinal series on August 12 revealed a slight lateral displacement of the duodenum. The radiologist felt that there was an extrinsic mass causing external pressure on the second portion of the duodenum and greater curvature of the stomach. Results of liver function tests were within normal limits.

When the patient first came under the author's observation on September 3, 1947, slight jaundice was noted. The temperature was normal, the pulse rate 80, and the blood pressure 122 mm. of mercury systolic and 80 mm. diastolic. There was some resistance in the right rectus abdominis muscle. Presence of a palpable mass in the right upper quadrant of the abdomen was uncertain.

Results of laboratory tests accorded with those previously carried out.

On September 23 the abdomen was opened through a right subcostal oblique incision. The gallbladder was noted to be rather thickened and with Hartman's pouch settled in a mass of adhesions in the area of the common duct. A wide curve involving the first and second part of the duodenum and over the head of the pancreas was observed. In this curve of the duodenum a hard, irregular mass about the size of a small lemon was felt. It appeared to be fairly well delineated from the body and tail of the pancreas. The tissue circumjacent to this mass, which included the common duct and retroperitoneal tissues, was brawny and edematous as if involved in a prior existent inflammatory process of some type. Frozen section from the mass revealed inflammatory tissue. It was considered that it was best not to take a chance that the mass was totally inflammatory, which meant that a resection should be done. This was accordingly carried out in a single stage partial pancreaticoduodenectomy. Postoperative convalescence was uneventful.

The pathological report was "Pancreatic necrosis with cyst formation and pancreatitis."

* * *

CASE 2: The patient was a male 42 years of age. The chief complaint was progressive jaundice, severe itching of skin and loss of weight over a period of three weeks. The patient had been a heavy drinker for several years but had had no alcohol for the past year.

The last week in December, 1947, diarrhea developed with five or six loose stools daily, normal in color. One week later, jaundice developed with definite fading in color of stools. In January 1948, diarrhea recurred with mild abdominal cramps. The stools were normal in color. In May 1948, progressive painless jaundice with severe itching of the skin developed and there was progressive loss of weight.

Upon physical examination it was noted that the temperature was 97.6°F. and the blood pressure was 138 mm. of mercury systolic and 90 mm. diastolic. There was intense jaundice and the sclerae were jaundiced. The liver edge was palpable two finger-breadths below the right costal margin.

Erythrocytes numbered 4,880,000. The hemoglobin value was 87 per cent. Leukocytes numbered 9,850 with normal differential of cells. There was a trace of albumin in the urine, but no sugar; six to eight leukocytes per high power field were noted, and occasional fine and coarse granular casts. A quantitative urobilinogen test was positive in 1:10 dilution. The icteric index was 50 units. There was 35 per cent retention of Bromsulfalein®. There was positive delayed reaction to van den Bergh's test, and a biphasic direct reaction. A quantitative test for bilirubin showed 1.8 mg. per 100 cc. Result of a cephalin-cholesterol flocculation test was negative. A test of the stool was positive for urobilin, negative for bilirubin.

The abdomen was opened through a right paramedian incision. The liver was found to be normal in size. It was smooth and showed no metastasis. It appeared to be congested with bile. The gallbladder was thin-walled, filled with black bile, and contained no stones. The common duct was thin-walled and distended. No stones were palpated in it. The head of the pancreas was enlarged, being about 2 cm. in diameter, and was very firm. It seemed to be freely movable. The remainder of the pancreas was fairly firm but otherwise normal. The fundus of the gallbladder seemed to lie most easily against the anterior surface of the stomach, so anastomosis was made between the gallbladder and the stomach just proximal to the pylorus. Recovery was uneventful and the jaundice cleared.

At a second operation, with the patient under continuous spinal anesthesia, a transverse upper abdominal incision was made, transecting both recti muscles. The omentum was found adherent to the old upper abdominal scar. After the omentum was freed the previous anastomosis was noted to be intact with very little peritoneal reaction about it. There were a few adhesions between the gallbladder and the transverse colon and between the liver bed and second portion of the duodenum. These were freed and the fingers introduced into the foramen of Winslow. By so doing, a large tumor mass could be felt in the head of the pancreas which seemed to be freely movable. This tumor was thought to be a carcinoma of the pancreas. A partial pancreaticoduodenec-

tomy was performed. The patient made uneventful recovery.

The pathological report was "Cyst, pancreas, simple obstructive; cholecystitis, subacute; lymphadenitis, regional."

DISCUSSION

In retrospect it might be said that in each of the two cases presented the clinical history might have indicated the true nature of the disease and that the suspicion of carcinoma of the head of the pancreas was unwarranted. Experience has shown, however, that the clinical history is not always to be trusted and that carcinoma of the common duct, carcinoma of the ampulla of Vater and carcinoma of the head of the pancreas may be associated with painless intermittent jaundice, painless constant jaundice and painful intermittent jaundice. Moreover, the pathological findings in each of these cases make it evident that the true nature of the disease could not be determined by gross examination at the time of operation.

SUMMARY

Two cases of pancreatic cyst causing obstructive jaundice are reported.

Partial pancreaticoduodenectomy was performed in both cases, leading to complete relief of symptoms.

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Anaphylactic Shock Following Intravenous Administration of Thiamine Chloride

Report of a Case

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Recently, severe reactions to vitamin preparations have been reported in the medical literature.[2, 3, 4, 5, 6, 7] Since these substances are currently popular and are used extensively, and as they may be potentially dangerous when employed indiscriminately, it is fitting to bring forth periodically for consideration by the medical profession certain representative cases of sensitization and to sound a word of caution.

CASE REPORT

A 39-year-old male had been given two intravenous injections of thiamine chloride for pain in the left shoulder by his wife, a nurse. After the second injection, the patient wheezed and noted some pruritus which disappeared shortly.

At 7 p.m. June 6, 1947, about four months after the second injection, a third injection of 10 mg. of thiamine chloride was administered intravenously. Within two or three minutes, the patient experienced difficulty in breathing and became cyanotic. The skin became cold and moist. The patient then started to wheeze, cough, and expectorate mucus and bloody sputum. He complained of pain in the chest and abdomen. He was hospitalized within an hour, and at this time the skin was ashen. The lungs were full of musical and coarse bubbling rales and coarse rhonchi. The blood pressure was 70 mm. of mercury systolic and 40 mm. diastolic, the pulse rate was 120, respirations 28 per minute, and rectal temperature 97° F. Blood plasma, epinephrine, and oxygen were given immediately. Around 10 p.m. copious, bloody, liquid stools were being passed and the blood pressure was unobtainable. Therapy was continued, and adrenal cortical hormone, vitamin K, and atropine sulfate were added. By 1 a.m. on June 7 the patient's color and pulse had improved, and 5 per cent dextrose in normal saline was substituted for the plasma. At 4 a.m. he was much improved, the blood pressure was 98 mm. of mercury systolic and 70 mm. diastolic, and the pulse rate was 108. The bloody diarrhea and some abdominal cramping persisted, but they seemed relieved by Kaopectate® orally. By noon on June 7, the lungs had cleared, the color of the skin was normal, and the blood pressure was 128 mm. of mercury systolic and 80 mm. diastolic. Later in the afternoon a tarry stool was passed. Up to that time the patient had been given 1,500 cc. of blood plasma, 1,000 cc. of 5 per cent dextrose in normal saline, and 3 cc. of 1:1,000 epinephrine, most of which had been given in the first five hours after entry.

On June 8, 1947, 36 hours after the thiamine chloride injection, the pulse, temperature, respirations, and blood pressure were normal. The patient was taking water by mouth, and was able to breathe outside the oxygen tent without difficulty. He was discharged on June 10 ambulatory and asymptomatic with no gross evidence of blood in the stool.

Subsequent intradermal or passive transfer tests were not carried out. At last report a year later, the patient had remained in good health. There was no history of previous allergic disease in the patient or in his family.

COMMENT

The profound reaction of this patient to parenteral thiamine chloride was more severe than usual, although deaths from anaphylactic shock have resulted from the use of this drug. The many symptoms are indicative of the widespread involvement of the tissues affected in shock. In addition to circulatory collapse, there was clinical bronchial asthma with pulmonary edema and massive hemorrhage into the gastrointestinal tract. In a case reported by Reingold and Webb[5] microscopic changes noted at autopsy included constriction of the smooth muscle of the pulmonary arteries and bronchioles, which was accompanied by pulmonary engorgement, dilatation of the right side of the heart, and pulmonary emphysema. The presence of pigmented macrophages was thought to indicate that previous hemorrhages had followed an anaphylactizing injection. The veins and sinusoids of the visceral organs were found to be engorged with blood.

In spite of the potential danger of administering vitamin preparations by injection, especially intravenously, apparently this method of administration is widely used. Although such injections may be necessary in selected patients and of psychic advantage in some instances, the oral route remains the cheapest and safest for the great majority of patients.

Every prospective recipient of parenteral vitamin preparations should be quizzed as to sensitivities and reaction to previous similar injections. In addition the use of intracutaneous tests may indicate hypersensitivity to the substances. Even during the using of them, such symptoms as sneezing, wheezing, pruritus, nausea, vomiting, swelling, shortness of breath, nervousness, tachycardia, and collapse should indicate impending danger and perhaps a change in the route of administration of the preparation.

Necessary treatment of reactions depends on the severity of them. In the case here reported, parenteral antihistaminic drugs, which were not available at the time, would have been indicated, in addition to the measures used. In less fulminating cases, epinephrine has proved adequate.[1, 5]

SUMMARY

A case of anaphylaxis following the intravenous injection of 10 mg. of thiamine chloride is presented. The importance of determining sensitivity prior to parenteral administration of the substance is stressed. Oral administration of vitamins is the safest and preferable in a great majority of subjects. Anaphylactic shock was successfully treated with epinephrine, oxygen, blood plasma, and atropine.

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Allergic Parotitis

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THIS report is offered as further evidence that structures other than the respiratory tract, the gastrointestinal tract and the skin are subject to allergic disturbance. Such is the case in allergic disease of the parotid glands which, since first reported in 1925,[2] has been noted frequently.

Allergic parotitis affects all age groups. Cases in patients as old as 70[5] and as young as 2½ years[10] have been reported. Frequently a family history of allergic disease is noted.[10] Associated allergic disease has been observed in most well documented cases[3, 11, 12] and the presence of it certainly strengthens the diagnosis. Asthma,[5, 9, 11] urticaria, angioneurotic edema and allergic rhinitis[3, 5, 9, 12] all occur in conjunction with this condition. Specific sensitivities are varied but most patients who have the disease are sensitive to environmental allergens and to certain foods. Allergic reaction to pollens, however, is infrequently reported.[11] Sometimes an item of food will specifically precipitate an attack[12] but a seasonal history has not been reported. In the typical case, acute swelling develops either in relation to meals or upon arising in the morning. The importance of the inhalant factor may be observed in a case reported by Zindler and Frazer[12] in which attacks were precipitated when the patient handled live turkeys. In a case observed by the author, swelling developed when the patient opened a trunk full of old clothes.

The parotid swelling may involve one or both sides.[6, 12] It develops quite rapidly and lasts for from a few hours to several days. Pain is infrequent but patients may complain of a tense feeling in the cheeks, occasionally in the ears, and inability to open the jaws completely. Edema of the gland, the duct or both may occur[11] and some patients experience immediate relief following a spurt of saliva into the mouth. When examined during an attack, the gland is palpable but usually soft and non-tender. The orifice of Stensen's duct does not appear abnormal and clear saliva may be milked out. A stained smear of parotid secretion will often show many eosinophils, although their presence is not essential for diagnosis. X-ray studies of the area should be carried out in all cases, but instillation of Lipiodol® is indicated only when the diagnosis remains in doubt. Prompt response to epinephrine or an antihistaminic drug is strongly indicative of allergic reaction as a cause for the symptoms.[2, 6, 10, 12]

Differential diagnosis should not prove difficult in most cases of intermittent, painless parotid swelling of allergic origin, but iodine medication may be overlooked as a causative agent. Although the swelling may be the result of low-grade infection, in such cases pain and purulent secretions usually develop during the course of the disease. Mumps should offer no problem in differentiation, although a recurrent type of swelling associated with low-grade fever and lymphocytosis is reported in children.[1] Tumors, calculi and Mikulicz's disease secondary to sarcoid, lymphomata, etc., are distinguishable by characteristic findings. Cases of recurrent parotitis with no determinable cause have been reported,[4, 7] and it is conceivable that they might have been explained on a basis of allergic reaction had attention been drawn to the possibility.

Treatment of allergic parotitis consists principally of desensitization with specific allergens as determined by skin testing and substantiated by a careful history of allergic reactions. Significant foods should be eliminated from the diet whether the evidence of their culpability arises from the history or from the skin tests. Antihistaminics appear to be of non-specific, symptomatic value. The use of iodides for concurrent asthma is not advisable.

CASE REPORTS

CASE 1: A 49-year-old woman, the wife of a physician, was first observed by the author in May 1942. At that time she had had migraine for 15 years and angioneurotic edema and hay fever from which she had been free for five or six years. Since the fall of 1941, she had had bronchial asthma almost continuously. Associated with it were sneezing, stuffiness of the nose and itching of the ears. The patient noted that the symptoms subsided when she left her home in the San Fernando Valley and visited Los Angeles. One week previously, after years of relief, a combination of urticaria and angioneurotic edema involving the entire body developed suddenly. The condition lasted three days and subsided spontaneously.

There were no other significant symptoms except that, although the patient had no food dislikes, she had abdominal cramps and diarrhea whenever she ate peaches. She also noted that certain toothpastes caused her lips to swell. Her mother, father, three siblings and two children all had hay fever. There were no animals about the house and she used feather pillows.

Physical examination showed the nasal mucous membrane to be pale and edematous, the turbinates hypertrophied. Airspaces were ample and there was little discharge. No polypi were observed. The chest was clear except for occasional faint wheeze on expiration. No other abnormalities were noted. Complete tests disclosed pronounced reactions to significant pollens, epidermal materials, and foods. Treated perenially with alternating spring and fall pollens, advised as to environmental control and given a list of foods to eliminate from the diet, the patient since has been free of asthma and only rarely has mild, evanescent rhinitis and urticaria.

In 1946, swelling in the right parotid region developed suddenly while the patient was eating lunch. This subsided in three hours. Since then, the swelling has recurred four to five times a week, usually during or immediately after meals, especially breakfast. Associated with it is an odd stiff sensation of the cheek but no pain. Occasionally the right ear becomes plugged as well. The patient found that massaging the parotid area increases the swelling. Occasional sudden relief has occurred, accompanied by a spurt of saliva into the mouth. By careful observation, the patient has incrim-

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inated eggs and spices, especially pimientos and green peppers, as causing the swelling, but elimination of these foods from the diet has not reduced the episodes significantly. The parotid ducts have been probed and x-ray studies made but there were no untoward findings in either instance. The patient herself has found that an antihistaminic will cause the swelling to subside almost immediately. Recently, the most severe attack occurred when she opened an old trunk filled with clothes. Since the history of parotid swelling was first obtained, the gland has been examined and found both palpable and visibly swollen. Smears of secretions from Stensen's duct have shown only occasional epithelial cells but never eosinophils. The patient is practically free of the other symptoms of allergic disease, but the parotid swellings continue.

* * *

CASE 2: The patient, aged 52, wife of a physician, was first observed by the author April 27, 1948, because of asthma and bilateral swelling of the face. Fourteen years before, urticaria and angioneurotic edema had begun, with massive swelling of the lips, lids, and external genitalia, and no specific cause could be found. At the same time, perennial asthma and nasal blockage with rhinorrhea developed.

Parotid swelling on both sides had begun in 1947. This was usually sudden in onset and was associated with an increase in saliva and a pulling at the angles of the jaws, which interfered with eating. Except for dull aching, there was no pain. such episodes lasted a few hours to a few days, then subsided slowly. The attacks followed one another with increasing frequency until the patient was rarely free of symptoms. Wheezing had been noted as each episode developed. There were no symptoms relative to the gastrointestinal tract and the attacks of parotid swelling were not associated with season or location. The patient suspected that one attack was caused by the ingestion of crab, and she had also observed that the asthma was worse when she was at her beach home where many cattle grazed.

The past history, except for two operations on the sinuses, had no bearing on the complaints. A son has urticaria and a morning cough. The patient disliked peanut butter but ate all other foods. She slept on pillows with allergen-proof casings, but kept a dog and had wool rugs and ozite pads in the bedroom.

Upon physical examination the patient was observed to be alert and well nourished. The face was quite round, due to swelling over the rami of both mandibles. The parotid glands were large, soft and non-tender. The ducts could not be felt but saliva could be expressed with ease by external pressure. The nasal mucous membrane was pale and edematous, the turbinates large but airways adequate. Nasal secretion was abundant and clear mucoid in character. No abnormalities were noted in the remainder of the examination. Examination of the parotid secretions initially showed many leukocytes, of which 75 per cent were eosinophils. The saliva, however, was not grossly purulent. X-ray films of the parotid areas showed no evidence of calculi. In several subsequent examinations of the parotid secretion, eosinophilia was not again present.

The patient was skin-tested, and very large intradermal wheals developed as reaction to many but not selective pollens, epidermal materials, and foods.

In considering therapy, it was necessary to study the pattern of both the asthma and the parotitis. While the seasonal component was lacking, it was felt because of the skin reactions that pollens probably played a part important enough to warrant treatment. The character of the asthma suggested an environmental etiologic factor. Clinically, the parotitis did not show clear-cut relation to foods and there was every reason to believe that inhalant factors were important. The food reactions, however, could not be disregarded and the suspect items were accordingly eliminated from the diet. Antigens for pollen and epidermal materials were used, and environmental control was effected. Although admittedly complex, the treatment was decided upon as a result of deduction from facts. Treatment was begun in the middle of May. A letter from the patient's husband early in June reported that the asthma, while evident, was not so severe as to necessitate the use of epinephrin, and the parotid swelling had disappeared entirely. The letter emphasized the enormous psychological "lift" which the patient had experienced. Regular letters have reported satisfactory progress, with subsidence of the asthma and absence of parotid swelling except for four episodes all controlled by either pseudo-ephedrine or an antihistaminic. It is interesting that the most recent episode of parotid swelling, the first in several months, developed while the patient was preparing a dish of cracked crab, even though she wore rubber gloves as a precaution. At last report the patient remained well under continued treatment as outlined.

SUMMARY

Two cases of recurrent parotid swelling of allergic nature have been presented and the literature on this subject reviewed.

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California MEDICINE

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EDITORIALS

Catastrophe Coverage

One criticism which proponents of socialized medicine have leveled at voluntary programs of sickness cost insurance has been that the long-term chronic diseases are not covered, that the member suffering from a condition which by its very nature is bound to last a long time cannot receive care for the disease under the voluntary plans.

Voluntary sickness cost insurance is a relatively new member of the insurance family in the United States and, from all indications, a lusty, growing child. Both the physician-sponsored and the medical association non-profit plans have undergone a tremendous growth within a space of only a few years. As witness, our own California Physicians' Service has grown from 125,000 to more than 900,000 beneficiary members in less than five years.

With the growth in membership, C.P.S. and other voluntary plans are in a position to delve into new and unexplored types of coverage, their ability to do so springing from the fact that their financial position is secure to the point where a potential loss from a new type of service may be absorbed by the regular program. In this way a number of innovations have been developed, founded on actuarial experience and offered on an economically indicated basis which has later proved to be accurate in the light of experience. Such progress furnishes additional actuarial material as a basis for still further advances.

Latest item in this progressive movement is the announcement by California Physicians' Service of the addition of catastrophe coverage to its group contracts. For a small addition to the regular monthly dues, C.P.S. is now offering medical and surgical care for a list of 23 diseases or conditions for a period of a full two years or to a maximum expenditure of $5,000, whichever is reached first. The diseases covered are cancer, poliomyelitis, rheumatic fever, diabetes, osteomyelitis, tuberculosis and others in the chronic disease classification. The conditions include severe fractures and severe burns.

Here is pioneering at its best. C.P.S. does not know what the cost of this offering will be; however, it believes it knows this cost closely enough to warrant offering this new coverage to its members. If the advance calculations prove to be wrong, changes will have to be made; on the other hand, if the program can more than carry itself financially, it will be possible to add to it in service or to reduce the dues paid for it. Thus the beneficiary members stand to gain in service if experience proves the accuracy of the advance actuarial calculations; they will not be called upon to underwrite a deficit if the cost of care turns out to exceed the dues paid during the trial period.

California Physicians' Service has already been showered with nationwide acclaim for taking this momentous forward step. Its experience will be closely watched and its program will certainly set a pattern for all voluntary programs. Congratulations to those who studied the possibilities of catastrophe coverage, who worked out the methods of providing the coverage and who had the courage to introduce this latest advance in the voluntary systems of sickness cost insurance.

Industrial Fees for 1950

California physicians have been discussing—and cussing—for a number of months the fact that no established fee schedule was available to cover industrial accident cases. The 1946 fee schedule expired, by order of the Industrial Accident Commission, on June 30, 1949. The California Medical Association's proposed 1949 schedule was not commonly accepted by the bulk of the compensation insurance carriers, and physicians were left in the position of filing claims for their services in practically all cases.

The presentation of a new proposed fee schedule to the Industrial Accident Commission in December 1949 met with no success. The claims filed with the Commission were slow in being heard and relatively few in number, so that the vast majority of physicians were in a position of issuing bills at one level and receiving collections at a lower level. Naturally, a chaotic condition prevailed.

Meanwhile, representatives of the C.M.A. and of the insurance carriers were essentially in agreement on the level of fees which should be made effective for 1950. A further presentation was made to the Industrial Accident Commission, which on February 8 approved the new schedule as a "rule of court" to apply in cases which may come before the Commission. This is as far as the legal powers of the Commission extend; it is also as far as could be expected, which is far enough to make the schedule commonly accepted by both physicians and insurance carriers.

At long last, a new 1950 industrial fee schedule is a fact. As it is recognized by the Association, by the compensation insurance carriers and by the Industrial Accident Commission, there seems no reason to believe it will not be universally applied by all parties.

The new schedule is not perfect. It does not represent all that the Association wanted or asked. It does not meet the requirements claimed by some medical specialty groups and some geographical medical groups. On the other hand, it recognizes a level of fees which will mean substantially higher fees in close to 90 per cent of all industrial accident cases and some increase in the remainder.

Beyond that, the new 1950 fee schedule is based upon an arrangement with the compensation insurance carriers under which continuing meetings will be held between representatives of the C.M.A. and of the carriers. The joint committees which will henceforth be in existence will study all aspects of the compensation medical care field and will arrange for periodical reviews of the fee schedule. Thus, in a friendly atmosphere, inequities in the newly-adopted schedule may be corrected and alleged abuses may be investigated and settled. For the first time in the 37-year history of compensation insurance in California, machinery has been provided to keep industrial medical care under continuous study and scrutiny.

The new fees, by and large, are a most satisfactory advance over the former fees. The working relationship between physicians and insurance carriers is a milestone on the way to better conditions throughout the entire field.

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C. M. A. Statement of Principles
ON THE MEDICAL AND HOSPITAL CARE OF INDIGENTS BY COUNTIES

The following statement was adopted by the Council of the California Medical Association at its regular meeting January 14, 1950.

STATEMENT OF FACTS

1. The residents of counties in California are morally and legally obligated to provide medical care and hospitalization for those persons residing in the county who are unable to secure such care through their own resources.

2. To provide such service, it has been the custom of the counties, with few exceptions, to maintain a county hospital, in which are located beds for the care of the indigent sick, surgical facilities for those who need them and, in many instances, clinic facilities for the care of ambulatory patients.

3. It has also been the custom of most counties to provide both hospital bed and clinic facilities on the basis of maximum demand; such facilities are often not in use because the morbidity rate is below the maximum anticipated.

4. The provision of maximum demand facilities has not constituted a financial strain on the counties until recent years, when construction costs have risen materially. Inasmuch as the counties are legally required to keep their bonded indebtedness within a fixed maximum, the provision of additional hospital and clinic facilities at this time represents an extremely difficult financial operation, often impossible.

5. At the 1949 session of the State Legislature, A.B. 916 was enacted as Section 202 of the Welfare & Institutions Code. This law provides that the counties may contract with private individuals and institutions for the medical and hospital care of those indigents who are legally entitled to be given such care at the expense of the counties. This law makes it possible for the county governments to utilize the facilities of private hospitals and private medical care facilities (doctors' offices) in caring for eligible indigents and thus save (a) capital investments in facilities and (b) prolonged expensive hospital sojourns.

6. There exist in California today some 271 private hospitals with 48,829 beds for sick patients, many of these institutions having clinic facilities for the care of ambulatory patients. There also exist some 12,000 offices of private physicians capable of and licensed to treat ambulatory patients.

7. There exists in California today an organization of more than 10,000 physician members, California Physicians' Service, capable of contracting with county governments for the out-patient medical care of county indigents.

8. There exist in California today two hospitalization organizations, Hospital Service of California and Hospital Service of Southern California, both being non-profit organizations of hospitals capable of contracting with county governments for hospital care of county indigents.

CONCLUSIONS

1. Present construction costs make unwise the building of more county hospital facilities, either beds or clinic quarters, at this time unless urgently needed. Construction is only the beginning—maintenance goes on forever.

2. The maintenance of large county hospital facilities is a continuous financial drain on taxpayers.

3. The cost of operating county hospitals, including the maintenance of maximum facilities, is considerably higher than the comparable cost of private hospitals per patient per day.

4. The cost of operating county hospital clinic or out-patient facilities, including the maintenance of maximum facilities, makes for a high per-patient cost for the care provided.

PRINCIPLES

1. Additional county hospital construction in California, except for possible additional beds for the acute sick, is not needed at this time.

2. The counties should avail themselves of the provisions of Welfare & Institutions Code, Section 202, in contracting for the care of their indigent charges.

3. The facilities of the two hospitalization organizations and of California Physicians' Service should be utilized to the full by the counties in contracting for hospital and medical care for their eligible indigents.

4. The counties must retain the obligation of providing a social service screening of county residents for the determination of eligibility to receive these contracted services.

5. The counties should carefully survey the available medical and hospital care facilities within their own borders prior to seeking state or federal funds or incurring additional bonded indebtedness for added hospital construction.

Council Meeting Minutes

367th Meeting

Tentative Draft: Minutes of the 367th Meeting of the Council, Los Angeles, January 14, 1950.

The meeting was called to order by Chairman Shipman in Conference Room No. 8 of the Biltmore Hotel, Los Angeles, at 9:30 a.m., Saturday, January 14, 1950.

Roll Call:

Present were President Kneeshaw, President-elect Cass, Speaker Alesen, Vice-Speaker Charnock, Councilors Shipman, MacLean, Ball, Crane, Henderson, Anderson, Ray, Montgomery, Lum, Pollock, Green, Bailey, West, Frees and Thompson, and Editor Wilbur.

Absent for cause: Secretary-Treasurer Garland.

A quorum present and acting.

Present by invitation were Executive Secretary Hunton, Assistant Executive Secretary Wheeler, Legal Counsel Hassard, Field Secretary Clancy, Messrs. Clem Whitaker, Jr., and Ned Burman of public relations counsel, Dr. Wilton L. Halverson, State Director of Public Health, county society executive secretaries S. K. Cochems of Los Angeles, Glenn Gillette of Fresno, Vance Venables of Kern, K. C. Young of San Diego and William O. Tobitt of Orange; Dr. Lowell S. Goin, president, and Mr. William M. Bowman, executive director of California Physicians' Service; Drs. E. Vincent Askey, J. Lafe Ludwig, Louis Regan, John Ruddock, Eugene Hoffman, Sam J. McClendon and Clarence Rees; Mr. Ritz Heerman.

1. *Minutes:*

(a) On motion duly made and seconded, minutes of the 366th meeting of the Council, held November 20, 1949, were approved.

(b) On motion duly made and seconded, minutes of the 217th meeting of the Executive Committee, held December 14, 1949, were approved.

(c) On motion duly made and seconded, minutes of the 218th meeting of the Executive Committee, held December 22, 1949, were approved.

2. *Membership:*

(a) A report of membership as of January 13, 1950, was received and ordered filed.

(b) On motion duly made and seconded, five members whose 1949 dues had been received since the last Council meeting were voted reinstatement.

(c) On motion duly made and seconded in each instance, six applicants were elected as Associate Members. These were:

Alameda County: Melvin B. Black, Catharine Eastman, Benjamin A. Kogan, Reinhard B. Lewis.

San Francisco County: Irene A. Heindl, Lloyd E. Wilson.

(d) On motion duly made and seconded in each instance, seven applicants were elected to Life Membership. These were: Howard R. Parker, Alameda County; Lloyd Mills, Los Angeles County; L. B. Barnes, Placer-Nevada-Sierra County; R. R. Root, Riverside County; Burt F. Howard and Charles I. Titus, Sacramento County; and J. M. O'Donnell, San Benito County.

(e) On motion duly made and seconded in each instance, ten applicants were elected to Retired Membership. These were: Harry Auslen and Frank W. Redmonds, Alameda County; John W. Bumgarner and George W. Sweetser, Contra Costa County; George Berger, John W. Robinson and Raymond G. Taylor, Los Angeles County; Eleanor B. Rodgerson, Sacramento County; Lyman Elanson Thayer, San Bernardino County; Elmer J. Chesbro, Santa Clara County.

(f) On motion duly made and seconded in each instance, eleven applicants were granted a reduction of dues because of illness or postgraduate study.

3. *Financial:*

(a) A report showing bank balances and other items as of January 13, 1950, was received and ordered filed.

(b) On motion duly made and seconded, an appropriation of $5,000 originally made in 1948 to the Committee on Medical Economics, and not expended, was reaffirmed as applicable to the 1949-1950 fiscal year.

4. *Industrial Fee Schedule:*

President Kneeshaw summarized the meetings and other actions leading up to the adoption by the Executive Committee of a new schedule of fees for industrial accident cases and there was general discussion. The proposed new schedule has been approved by representatives of insurance carriers and has been presented to the Industrial Accident Commission for approval.

After considerable discussion, it was regularly moved, seconded and voted that the decision and actions of the Executive Committee be ratified by the Council, with the understanding that no fees in the new schedule be at levels lower than those in the 1946 schedule adopted by the Industrial Accident Commission.

Doctors Pollock and Thompson voted in the negative.

The Chairman called attention to the fact that a permanent committee is to be appointed to meet with a similar committee from the insurance carriers. He stressed the importance of a careful selection of the membership of this committee and asked all members of the Council to consider this matter and be prepared at the next meeting to present nominations.

5. *California Physicians' Service:*

Dr. Lowell S. Goin, president of California Physicians' Service, reported on the establishment of a

new committee in C.P.S., composed of chairmen of standing committees and meeting the day before board of trustees meetings; this has resulted in increased efficiency in board actions. He also reported that as of December 31, 1949, C.P.S. has approximately 875,000 beneficiary members and 10,326 physician members. Dr. Goin stated that under new legislation C.P.S. can deal directly with boards of supervisors for the ambulatory care of county indigents and that 16 county medical societies have shown an interest in establishing such a system; C.P.S. prefers that the county societies initiate interest and action in such instances.

Dr. Goin reported that C.P.S. is now negotiating with the Veterans Administration for an increase in the fees allowed for office and home visits. He also stated that C.P.S. is now considering the issuance of catastrophic contracts, to provide two years of care for a list of some 30 diseases or conditions. This would be issued as a rider to existing contracts.

Mr. Bowman discussed the balance sheet of California Physicians' Service as of November 30, 1949, and the operating statement for the eight months ended November 30, 1949. He pointed to the administrative cost for that period of 12.9 per cent, compared with an average of 13.29 per cent for the 15 prepayment plans of 200,000 or more enrollment, the largest of which had an administrative cost in excess of 20 per cent.

Dr. Goin summarized the report made by business analysts of the C.P.S. operations, the report showing notable improvement since an earlier study made in 1946-1947 and pointing to better operating conditions and an earnest endeavor by C.P.S. to follow sound business principles.

6. *National Cancer Institute:*

Dr. Goin discussed the manner in which federal funds for cancer research, teaching and control are distributed and pointed to the merits and dangers in the present method of allocation. Dr. Halverson explained that the $162,000 in such funds available in California is spent in conformity with plans worked out between the State Department of Public Health and the Association's Cancer Commission.

7. *State Department of Public Health:*

Dr. Halverson discussed the public health problems created by the presence of large numbers of migrant workers in the San Joaquin Valley, pointed to the high infant mortality rate in this group and stated that 26 per cent of the state's infant deaths occurred in a group of valley counties. His department plans a fly eradication program in controlled areas next summer as a means of determining if infant diarrhea may be minimized; he asked that the Association offer other suggestions. A letter from Councilor Anderson along these lines was referred to the Committee on Public Health and Public Agencies.

8. *Fees for Polio Cases:*

The question of payments to physicians for services in polio cases, where the National Foundation for Poliomyelitis assumes the cost of care, was discussed and it was regularly moved, seconded and voted to refer this to the Committee on Public Health and Public Agencies.

9. *Vocational Rehabilitation:*

A letter from Dr. Herbert I. Notkin, medical consultant to the Bureau of Vocational Rehabilitation of the State Department of Education, was read, the letter stating that the social servicing of applicants prior to the initial physical examination would represent a change in the bureau's policy and that the matter would be presented to the Medical Advisory Board of the bureau for consideration.

10. *Committee on Public Health and Public Agencies:*

Dr. Alesen gave a progress report and stated that legislation was being prepared to define more accurately the scope of activities of laboratory technicians and technologists. He also reported on a recent meeting with a committee from the California Conference of Local Health Officers, at which progress was made in arriving at acceptable definitions of the scope of activities of health centers and the practice of public health.

11. *Voluntary Health Insurance:*

Messrs. Eugene Robison, Gilbert Smith and Clarence Tookey appeared before the Council to request the cooperation of the Association in working out a fee schedule which could be considered a total fee for services provided to holders of commercial insurance policies below an accepted income ceiling. Dr. Ray reported on a meeting with insurance representatives in San Francisco along the same lines and it was agreed the special committee consisting of Doctors Lum, Ray and Ball should continue a study of the various proposals.

12. *American Public Health Association:*

Dr. Louis Regan reported on the recent annual meeting of the American Public Health Association, called attention to the organizational setup of this association and urged that members of the Association take a greater interest in the A.P.H.A.

13. *Academy of Forensic Sciences:*

Mr. Hassard called attention to the organization meeting of the Academy of Forensic Sciences, a national body interested in the replacement of the coroner system with a medical examiner system. On motion duly made and seconded, it was voted to appoint Dr. Louis Regan as the C.M.A. delegate to this meeting, to be held in Chicago, provided the Los Angeles County Medical Association will grant him the time to attend the session.

14. *Committee on Interns and Residents:*

Dr. J. Lafe Ludwig, chairman of the Committee on Interns and Residents, presented a report which

advocated the publication of a bimonthly brochure to be sent to medical students, interns and residents, at an estimated cost of about $3,000 annually. On motion duly made and seconded, this report was approved and the estimated funds appropriated for this purpose.

15. *Committee on Postgraduate Activities:*

Dr. John Ruddock, chairman of the Committee on Postgraduate Activities, announced the resignation of Dr. Carroll B. Andrews as director of the committee's program. On motion duly made and seconded, this resignation was accepted with regret and with an expression of appreciation for the valuable services rendered by Dr. Andrews; the date of resignation is February 1, 1950.

Dr. Ruddock proposed the appointment of Dr. Charles A. Broaddus of Stockton to succeed Dr. Andrews, appointment to be on the basis of half-time at a compensation of $500 monthly. On motion duly made and seconded, this appointment was voted.

Dr. Ruddock also requested that clerical help be secured for Dr. Broaddus on a full- or half-time basis and on motion duly made and seconded, such employment was approved.

Dr. Ruddock announced that the program of his committee would be aimed at providing postgraduate opportunities for all members of the Association, in urban as well as rural areas.

16. *Weimar Sanitarium:*

The report of a special committee to review the medical care program of Weimar Sanitarium was considered and on motion duly made and seconded, it was voted to approve this report and to forward a copy to the board of supervisors in each county which participates in the operation of the institution.

17. *Committee on Medical Education and Medical Institutions:*

A report of the committee, recommending against the approval of Association members serving as faculty members in a proposed school for drugless practitioners, was read and discussed. On motion duly made and seconded, the report was approved.

18. *Nursing:*

Dr. Kneeshaw reported on a meeting held with representatives of the California State Nurses Association at which matters of mutual interest had been discussed. He recommended that a committee be appointed to meet with a similar committee of the C.S.N.A. when similar matters occur and on motion duly made and seconded, it was voted that the Chairman appoint such a committee.

A statement of the Association's attitude on nursing, ordered by the Executive Committee, was read and discussed. It was agreed that copies of this statement be sent to all members of the Council for consideration prior to the next meeting.

19. *Legal Department:*

Mr. Hassard discussed several developments in medicolegal considerations, including a recent decision by the California Supreme Court holding that expert opinion is required in technical professional liability proceedings and that common knowledge is not sufficient in such cases. He also suggested that the California delegates to the American Medical Association take steps to bring about the creation of a department within the A.M.A. which could analyze and advise in advance on proposed federal appropriations for medical services. He also discussed the import of the new lobbying law adopted by the 1949 special session of the Legislature.

20. *Public Relations:*

Clem Whitaker, Jr., reported that the Association's radio program, "California Caravan," has reached a new high listener rating. He also stated that a press conference recently held by a physician who had just returned from Europe had been most successful and urged that other physicians who have had an opportunity to study state medicine firsthand plan to hold similar press conferences.

21. *Public Policy and Legislation:*

Dr. Cass reported on a meeting held in Denver on January 7, attended by representatives of 21 western state medical associations, at which several resolutions were adopted relative to pending federal legislation. On motion duly made and seconded, it was voted to prepare a resolution for California delegates to introduce in the A.M.A. House of Delegates to provide for the strengthening of the Washington office of the A.M.A.

22. *California State Board of Nurse Examiners:*

A request from the California State Board of Nurse Examiners, for the nomination of two candidates for the appointment of one as a member of an advisory board, was read. It was regularly moved, seconded and voted that the Chairman make two nominations.

23. *A.M.A. Industrial Health Conference:*

An invitation to attend an industrial health conference scheduled by the American Medical Association was discussed and it was regularly moved, seconded and voted that Dr. C. Kelly Canelo be sent as an official delegate to this meeting.

24. *Los Angeles Anatomical Institute:*

An application of the Los Angeles Anatomical Institute for approval by the Association was discussed and it was regularly moved, seconded and voted to refer it to the Executive Committee.

25. *Student Nurse Recruitment Program:*

On motion duly made and seconded, it was voted that the Chairman appoint a representative to serve

on a committee of nursing, nursing school and hospital representatives.

26. *Santa Clara County Medical Society:*

A request for financial participation in a public relations campaign of the Santa Clara County Medical Society was discussed and on motion duly made and seconded, it was voted to postpone action on this matter to the next meeting.

27. *Time and Place of Next Meeting:*

The next meeting will be held in San Francisco on Sunday, March 19, 1950, following the March 18 Conference of County Medical Society Secretaries.

Adjournment.

There being no further business to come before the meeting, it was adjourned at 6:20 p.m.

SIDNEY J. SHIPMAN, M.D., *Chairman*
L. HENRY GARLAND, M.D., *Secretary*

Executive Committee Minutes

217th Meeting

Tentative Draft: Minutes of the 217th Meeting of the Executive Committee, San Francisco, December 14, 1949.

The meeting was called to order by Chairman MacLean in Room 218 of the St. Francis Hotel, San Francisco, at 6:30 p.m., Wednesday, December 14, 1949.

Roll Call:

Present were President Kneeshaw, Council Chairman Shipman, Auditing Committee Chairman MacLean, Secretary Garland and Editor Wilbur. A quorum present and acting.

Present by request were Executive Secretary Hunton and Legal Counsel Hassard. Present by invitation were Drs. Frank J. Cox, Victor Dillon and A. B. Sirbu, representing the Western Orthopedic Association; Avery Hicks, representing ophthalmology; Ralph Teall, president of the Sacramento Society for Medical Improvement; Wayne Pollock, Councilor of the Eighth District; M. L. Skaggs and William B. Neff, anesthesiologists.

1. *Industrial Medical and Surgical Fees:*

Mr. Hassard was asked to review the history of medical and surgical fees for industrial injury cases and discussed the basis on which such fees had been established since the first fee schedule was adopted in 1913. Thereafter there was discussion on the schedule of fees arrived at by compromise between the subcommittee of the Executive Committee (Drs. Kneeshaw, Cass and Garland) and representatives of the compensation insurance underwriters. Objections to the approval of such a schedule or its offer to the Industrial Accident Commission for approval were voiced by the orthopedists and by the Sacramento Society for Medical Improvement. Both asked that a longer time be allowed for a more thorough study of the schedule by their groups. Dr. Hicks voiced disapproval of two specific items in the proposed schedule and Drs. Skaggs and Neff asked that certain changes be made in the schedule items affecting anesthesiology.

2. *Executive Session:*

At this point the Executive Committee went into executive session, at which time it was agreed that the subcommittee which had dealt with the insurance representatives had had authority to act, that it had acted in good faith and that good faith demanded the presentation of the schedule to the Industrial Accident Commission for approval. It was further agreed that Dr. Kneeshaw should present the schedule to the Industrial Accident Commission at its meeting of December 15, 1949.

Adjournment.

There being no further business to come before the committee, the meeting was adjourned at 12:05 a.m., December 15, 1949.

H. GORDON MACLEAN, M.D., *Chairman*
L. HENRY GARLAND, M.D., *Secretary*

218th Meeting

Tentative Draft: Minutes of the 218th Meeting of the Executive Committee, San Francisco, December 22, 1949.

The meeting was called to order by Chairman MacLean in Room 212 of the St. Francis Hotel, San Francisco, at 2:00 p.m., Thursday, December 22, 1949.

Roll Call:

Present were President Kneeshaw, Speaker Alesen, Council Chairman Shipman, Auditing Committee Chairman MacLean and Secretary Garland. A quorum present and acting.

Present by request were Executive Secretary Hunton, Legal Counsel Hassard and Assistant Executive Secretary Wheeler.

1. *Industrial Medical Fees:*

A general discussion of the industrial medical fee situation was held and it was agreed that a letter be sent to the chairman of the insurance negotiating committee, outlining the basis of the proposed 1950 fee schedule.

On motion duly made and seconded, it was voted to send a copy of the 1950 fee schedule to secretaries of the county medical societies and to each member of the Association, with an appropriate foreword of explanation, such mailing to be made at the earliest practicable date. The Executive Secretary was instructed to send copies of the proposed foreword to all members of the Executive Committee for approval.

2. *Local Health Officers:*

On motion duly made and seconded, it was voted to notify the Committee on Public Health and Public Agencies that the Executive Committee considered it advisable to name one local health officer to each of the subcommittees of the main committee.

On motion duly made and seconded, it was voted to send a communication to the county medical societies to suggest that local health officers be invited to attend meetings of the county societies' councils, especially when matters relating to public health activities were to be subjects of discussion.

3. *Committee on Public Health and Public Agencies:*

It was agreed that a member of the standing Committee on Hospitals, Dispensaries and Clinics be added to the special Committee on Hospital Construction (Drs. Thompson and Anderson, Mr. Hassard) and Chairman Alesen of the Committee on Public Health and Public Agencies announced his intention to invite Dr. John C. Sharp of Salinas to accept such appointment.

4. *Secretarial Conference:*

After discussion it was agreed that the annual Secretarial Conference should be held in San Francisco on March 18, 1950, with the expectation that the Council would meet the following day. It was suggested that one or more county society executive secretaries be invited to discuss their county programs at this meeting.

5. *C.M.A. Mailing List:*

On motion duly made and seconded, it was voted to permit the California Academy of Sciences and the Department of Research and Statistics of the Industrial Accident Commission to use the Association's mailing list for approved literature.

6. *Payments for Poliomyelitis Care:*

Discussion was held as to the propriety of physicians accepting payments from national organizations for their care of poliomyelitis cases of non-indigent patients and it was agreed to discuss this matter further at the next Council meeting.

7. *Legal Department:*

Mr. Hassard reported on several legal matters, including the California Supreme Court decision in favor of a physician in a malpractice suit, the prosecution of anti-trust suits against two medical associations and the passage of new legislation by the special session of the State Legislature.

On motion duly made and seconded, it was voted to prepare a statement on the Association's attitude toward the practice of nursing, to be sent to the county medical societies and to members of the Legislature. Dr. Kneeshaw and Messrs. Hassard and Hunton were instructed to prepare such a statement for the approval of the Executive Committee.

On motion duly made and seconded, it was voted that a documented article be prepared for prominent publication in CALIFORNIA MEDICINE relative to health insurance and the interest of some public officials in it, such article to be reviewed before publication by present and former officers of the Association.

On motion duly made and seconded, it was voted to instruct legal counsel to prepare an article for publication in CALIFORNIA MEDICINE to clarify the provisions of the hypnotic drug law adopted by the 1949 Legislature.

On a question of medical ethics relating to a physician associating with a lay laboratory technologist, legal counsel was instructed to investigate the consideration of such matters by the Judicial Council of the American Medical Association.

8. *Care of War Veterans:*

It was regularly moved, seconded and voted to make a suitable announcement in the official Journal of the advisability of ascertaining from veterans any rights they might have under federal laws for private care by physicians and to notify the California Department of the American Legion to that effect.

9. *Employment of Executive Secretary:*

In executive session it was regularly moved, seconded and voted to extend for a period of three years starting May 1, 1950, the employment contract of the Executive Secretary, compensation to be at the present level, with the provision that within the next six months a designated appointee of the Executive Committee review the compensation received by officers performing similar duties with other organizations and businesses, with a view toward possible upward revision of compensation.

10. *Medical Economics:*

Dr. MacLean reported that the Alameda County Medical Association, through the Committee on Medical Economics of the California Medical Association, in its study of physician-patient relationships plans to secure the services of a business psychologist, who would make a study along these lines. The Alameda County Medical Association is underwriting the expense of this study, with the thought that the California Medical Association may wish to share in the contemplated $5,000 cost if the results appear to warrant such an appropriation. This sum has previously been appropriated by the Council for a study of physician-patient relationships which has been under way in the past two years.

11. *Additional Delegate to A.M.A.:*

The Secretary reported that the Association was entitled to eleven (11) Delegates and Alternates to the American Medical Association and that only ten (10) had so far been elected or appointed. The additional Delegate and Alternate would be entitled to serve on January 1 of the year following their election or appointment. On nominations duly made and seconded in each instance, R. Stanley Kneeshaw of San Jose was elected Delegate and Russel V. Lee of Palo Alto was elected Alternate, both to serve for the year 1950. It was pointed out that these offices for the term starting January 1, 1951, would be subject to election by the 1950 House of Delegates.

Adjournment.

There being no further business to come before the meeting, it was adjourned at 6:25 p.m.

H. GORDON MACLEAN, M.D., *Chairman*
L. HENRY GARLAND, M.D., *Secretary*

C.P.S. to Change Contracts and Fees Only Once Yearly

In order to avoid confusion and to permit better evaluation of any changes that are made, California Physicians' Service henceforth will make changes in contracts with beneficiaries and in fee schedules only once each year—at the meeting of the board of trustees on or after September 1. This policy, which was announced recently by Henry L. Gardner, M.D., secretary of C.P.S., in a letter to presidents of all county medical societies, was adopted by the board of trustees at its meeting in January.

"This action was taken," the letter explains, "because changes in the schedule and in our contracts have a very direct effect on our finances. Projections into the future cannot be made with any degree of accuracy without an adequate length of time to evaluate previous changes.

"We believe this will permit time not only for more adequate consideration of the schedule, but for study of the schedule in relation to existing contract rates and benefits for contemplated revision of contracts.

"Furthermore, we realize that changes are confusing to physician and beneficiary members alike, and making all necessary revisions at one specific time should make for smoother relationships.

"The Fee Schedule Committee functions on a continuing basis, and will continue to welcome suggestions from physician members. Their report will continue to be made at the annual meeting, but without the necessity for immediate action without due consideration."

In Memoriam

DRAPER, DAVID BURRIS. Died in San Jose, January 17, 1950, aged 55, of a heart attack. Graduate of St. Louis University School of Medicine, 1921. Licensed in California in 1922. Dr. Draper was a member of the Santa Clara County Medical Society, the California Medical Association, and the American Medical Association.

✤

LEWIS, FLOYD D. Died in Concord, January 24, 1950, aged 65, of lymphoblastoma and chronic myocarditis. Graduate of Willamette University Medical Department, Salem, Oregon, 1909. Licensed in California in 1921. Dr. Lewis was an Associate Member of the Alameda County Medical Association, and the California Medical Asspciation.

✤

MICHELSON, PAUL DANIEL, JR. Died in Berkeley, January 1, 1950, aged 56. Graduate of the College of Physicians and Surgeons of San Francisco, 1920. Licensed in California in 1920. Dr. Michelson was a member of the San Francisco County Medical Society, the California Medical Association, and the American Medical Association.

✤

MORRISON, WAYLAND AUGUSTUS. Died in Los Angeles, January 5, 1950, aged 61. Graduate of Harvard Medical School, Boston, 1914. Licensed in California in 1914. Dr. Morrison was a member of the Los Angeles County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

✤

PAGE, CLARENCE WINSLOW. Died in Berkeley, January 25, 1950, aged 70, of coronary occlusion. Graduate of Cooper Medical College, San Francisco, 1904. Licensed in California in 1904. Dr. Page was a member of the Alameda County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

✤

YOAKAM, FRANK ARTHUR. Died in Moorpark, January 5, 1950, aged 74, after a long illness. Graduate of the National Medical University, Chicago, 1902. Licensed in California in 1921. Dr. Yoakam was a retired member of the Ventura County Medical Society, and the California Medical Association.

NEWS and NOTES

NATIONAL • STATE • COUNTY

ALAMEDA

Pamphlets titled "How the Doctors in Alameda County Are Protecting You," describing the **facilities and services of the Alameda County Medical Association,** are being distributed to the public by the association. The pamphlet gives information on how to obtain the services of a qualified physician in an emergency, how to obtain medical care if there is no money to pay the doctor, how to protect the family budget against cost of illness, how to present medical care problems for solution or any complaint for action by the medical association.

A statement by the association accompanying announcement of the pamphlet said: "We want everyone to have the information contained in this booklet because the Alameda County Medical Association **guarantees medical care to all,** regardless of ability to pay, and we want people to know how to obtain this care when needed."

More than 75,000 of the booklets have been distributed through retail druggists who have wrapped them with packages, and by speakers who have handed them out to audiences.

CONTRA COSTA

Voters in the Concord Hospital District defeated a proposed bond issue to provide funds for building a **district hospital** with state and federal aid. Votes against the bonds were reported to have exceeded those for the issue by about 3 to 1. Following defeat of the proposal, it was announced that the board of directors of the Concord Community Hospital, a non-profit organization which is already in operation, will go forward with plans for improvement of existing facilities.

INYO

Dr. Victor H. Hough has been appointed full-time health officer for Inyo County, succeeding **Dr. Charles W. Anderson.** Dr. Hough's headquarters are at Independence.

LAKE

Dr. Selmes P. Funkhauser last month became health officer for Lake County, succeeding **Dr. M. C. Beil.** Dr. Funkhauser's headquarters are at Clearlake Highlands.

LOS ANGELES

The annual **Postgraduate Assembly of the College of Medical Evangelists** will be held on the Los Angeles campus of the medical school March 12, 13 and 14, at Paulson Hall, 1825 Michigan Avenue. More than 1,500 physicians from all over the United States are expected to attend.

Among guest speakers from outside the state are Dr. Jonathan Forman, professor of history of medicine, Ohio State Medical School, who will read a paper, "What About Vitamins?"; Colonel James P. Cooney, Division of Military Application, Washington, D. C., who will speak on "Medical Aspects of Radiological Defense"; Dr. Frank N. Allan, of the Lahey Clinic, Boston, who will discuss "Coma, Its Causes and Treatment"; and Dr. Carl G. Morlock of the Mayo Clinic and assistant professor of medicine, University of Minnesota, whose topic is "Current Concepts in Treatment of Duodenal Ulcer."

Medical professors from the University of California in Los Angeles, the University of Southern California, and other western medical schools, together with specialists and clinicians from the College of Medical Evangelists, will present lectures, panel discussions, scientific exhibits and motion pictures during the session.

SAN FRANCISCO

Dr. Lowell Rantz, associate professor of medicine at Stanford University School of Medicine, was elected president of the Western Society for Medical Research at that organization's third annual meeting in January. Dr. Rantz succeeds **Dr. Myron Prinzmetal** of Los Angeles.

* * *

Two **appointments to the faculty** of the University of California Medical School were announced recently. Dr. Dermott Brownrigg Taylor, formerly of the faculty of the University of London, was appointed associate professor of pharmacology, and Dr. Ralph Hawkins of Mill Valley was appointed lecturer in anatomy.

* * *

Two San Francisco physicians are to make overseas tours this year as participants in the Army Medical Department overseas consultant program, according to announcement last month by the Army Surgeon General. **Dr. Karl M. Bowman** is scheduled to leave July 5 for a tour of the Far East Command, and **Dr. James O. Gillespie** is to visit the European Command area next November.

GENERAL

A plan to cover **medical care costs** over an extended period for 23 diseases which by their nature often require long-continued treatment was announced recently by **California Physicians' Service.** By this action C.P.S. became the first non-profit health plan in the nation to offer coverage for so-called "catastrophic" illnesses.

The new "catastrophic coverage" provides greatly increased medical, surgical and radiological therapy services —up to two years or in the amount of $5,000—for persons with the following diseases: Cancer, tuberculosis, diabetes, poliomyelitis, osteomyelitis, rheumatic fever, brain tumor, congenital heart disease, pernicious anemia, severe fractures, Hodgkin's disease, goiter, hemophilia, Raynaud's disease, cirrhosis of the liver, malaria, undulant fever, coronary artery disease, paralysis, epilepsy, detached retina, severe burns, and leukemia.

Extension of coverage for these conditions at a small cost in monthly dues will be made on a group enrollment basis —either as additional protection for existing C.P.S. groups or as expanded coverage for new groups.

* * *

The board of regents of the **American College of Chest Physicians** has announced the offering of a cash prize award of $250 to be given annually for the best original contribution, preferably by a young investigator, on any phase relating to chest disease. The first award will be made at the forthcoming annual meeting of the College to be held

POSTGRADUATE EDUCATION NOTICES

American College of Physicians

Course: Internal Medicine.

Date: June 19 through 23, 1950.

Fee: A.C.P. members, $30.00; non-members, $60.00.

Contact: Stacy R. Mettier, M.D., F.A.C.P., Director, Medical Extension, University of California Medical Center, San Francisco 22, California.

College of Medical Evangelists, Graduate School of Medicine

Course: Endocrinology (8 periods).

Date: April 3 to May 22, 1950, Mondays 8:00 to 9:30 p.m.

Fee: $30.00.

Course: Thoracic Surgery (8 periods).

Date: May 3 to June 21, 1950, Wednesday 8:00 to 9:30 p.m.

Fee: $30.00.

Contact: H. M. Walton, M.D., Dean, Graduate School of Medicine, College of Medical Evangelists, 312 North Boyle Avenue, Los Angeles 33, California.

University of Southern California, Medical Extension Education

Course: Survey Course for General Practitioners.

Date: March 13, 1950, through March 17, 1950, five days, full-time.

Fee: $50.00.

Place: Los Angeles County Hospital.

Courses in Anesthesia to be arranged. General Review of Clinical Anesthesia; Basic Principles and Techniques. 12 weeks. Tuition $50.00 to $300.00.

University of California, Medical Extension

Course: Graduate Course in Ear, Nose and Throat Pathology.

Date: April 2 through 9.

Fee: $50.00.

Course: Internal Medicine and General Surgery.

Date: April 24 through 28.

Fee: $50.00.

Course: Psychiatry for the General Practitioner.

Date: April 24 through 28.

Fee: $50.00.

Contact: Stacy R. Mettier, M.D., Medical Extension, University of California Medical School, San Francisco 22, California. Fee and printed program supplied on request.

Stanford University School of Medicine

Course: Postgraduate conference in Clinical Ophthalmology, March 27 through March 31, 1950. Registration will be open to physicians who limit their practice to the treatment of diseases of the eye, ear, nose and throat. In order to allow free discussion by members of the conference, registration will be limited to 30 physicians. Instructors will be Drs. A. Edward Maumenee, Dohrman K. Pischel, Jerome W. Bettman, Earle H. McBain and Arthur J. Jampolsky. Programs and further information may be obtained from Office of the Dean, Stanford University School of Medicine, 2398 Sacramento Street, San Francisco 15, California.

in San Francisco June 22-25, 1950. Manuscripts submitted for the award must reach the office of the American College of Chest Physicians not later than May 1, 1950.

Additional information may be obtained from the executive secretary of the college, 500 North Dearborn Street, Chicago 10, Illinois.

* * *

Award of two **fellowships for research** in California hospitals was announced recently by the American Heart Association. One went to Joseph H. Miller, Los Angeles, for research on a mechanical heart-lung at Cedars of Lebanon Hospital, and the other to Ray H. Rosenman of Chicago for studies on hypertension at Mount Zion Hospital, San Francisco.

* * *

The national convention of the American Academy of Applied Nutrition and the American Anti-Arthritis Association will be held in Riverside on April 1 and 2, 1950.

* * *

The following resolution was adopted by the **California Society of Pathologists** at its semi-monthly meeting in December:

Resolved, That as a statement of policy the California Society of Pathologists is opposed to the centralization of facilities for the initial diagnosis of malignant disease by means of examinations of tissues, exudates, or bodily excretions by whatever name the procedure might be called. This is specifically meant to include any exfoliative cytologic diagnostic procedure proposed as a part of any mass survey conducted by federal, state or municipal government or political subdivision thereof or by any private organization sponsored or supported by such governmental agency or by endowments or public voluntary subscription; and be it further

Resolved, That exfoliative cytologic examinations incident to mass surveys be done at the local level by pathologists licensed to practice medicine in California. Should the local pathologist desire consultation, in accordance with usual custom, he may refer the material to any pathologist of his choice."

* * *

The California Medical Association has received the following communication from Dr. George F. Lull, secretary and general manager of the American Medical Association:

"On January 9, 1950, an estimate was made of all monies sent in by the various state and territorial medical associations in payment of the 1949 [A.M.A.] **assessment.** This shows that, percentagewise, your society stands Number 4 on the list of 53 constituent associations."

* * *

The Cancer Commission of the California Medical Association announces a **postgraduate (refresher) course on neoplastic diseases** for practicing physicians to be given Thursday and Friday, March 30 and 31, in Lane Hall, San

Francisco. The course will be conducted by Stanford University School of Medicine and University of California Medical School in cooperation with the California division of the American Cancer Society which is defraying the expenses of the course. Enrollment will be limited to 300. Applications should be mailed to Dr. David A. Wood, Secretary, Cancer Commission, California Division of the American Cancer Society, 467 O'Farrell Street, San Francisco 2, California, not later than March 23, 1950. The program for the two days follows:

THURSDAY

Ralph Byron, M.D., Chairman

8:30 a.m.—Introductory Remarks, David A. Wood, M.D., Secretary, Cancer Commission.

8:45 a.m.—Cancer Examination.

9:45 a.m.—Rectum and Colon—Robert A. Scarborough, M.D., and H. Glenn Bell, M.D.

10:30 a.m.—Recess.

10:45 a.m.—Breast—Leonard G. Dobson, M.D., and Robert S. Stone, M.D.

11:30 a.m.—Esophagus and Stomach—Leon Goldman, M.D., and Albert Snell, M.D.

1:45 p.m.—Lung—E. F. Holman, M.D., and H. B. Stephens, M.D.

2:30 p.m.—Lymphoblastoma—Michael Shimkin, M.D., and Warren Bostick, M.D.

3:30 p.m.—Recess.

3:45 p.m.—Chemosurgery—Richard Shepard, M.D.

4:30 p.m.—Stanford Tumor Conference.

FRIDAY

R. R. Newell, M.D., Chairman

9:00 a.m.—Uterus, Cervix and Corpus—Daniel Morton, M.D., and L. Henry Garland, M.D.

10:00 a.m.—Panel—Two Major Symptoms of Carcinoma—Bleeding and Cough—Norman Sweet, M.D., and Victor Richards, M.D.

11:15 a.m.—Visible Tumors — Glenn Bell, M.D., Frances Torrey, M.D., and Bertram Low-Beer, M.D.

2:00 p.m.—Experimental Advances in Diagnosis and Therapy of Cancer—Philip West, M.D., and Howard Bierman, M.D.

BOOK REVIEWS

ALLERGY IN RELATION TO OTOLARYNGOLOGY. By French K. Hansel, M.D., Editor-in-Chief, Annals of Allergy, Associate Professor of Otolaryngology, Washington University School of Medicine. A Panel Discussion. Bruce Publishing Company, St. Paul and Minneapolis, 1949. An Official Publication of the American College of Allergists, $2.50.

The first part of this book, which is edited by Dr. French K. Hansel, deals with the clinical side of allergic reactions as related to the respiratory tract. Particular stress is put on the nose and accessory sinuses. Dr. Hansel gives a thorough explanation of nasal cytology and emphasizes the tremendous importance of this diagnostic procedure. Six beautiful plates showing different grades of eosinophilia in the nasal secretions are presented.

In a discussion of the problem of tonsillectomy in children with allergic disease, it is emphasized that often the operation affords poor relief of symptoms. The question of allergic disease of bacterial origin is left open. A discussion of the pathology of allergic states is rather weak since the fundamental problem of changes in the small blood vessels is not discussed. But in general this part of the book makes very worthwhile reading and should impress upon any rhinologist that allergic disorders are of tremendous importance in his specialty.

In the latter part of the book, which is a panel discussion, differences of opinion are so pronounced as to indicate that individual interest may be concerned with only one phase rather than with the entire picture. One discussant, for example, tends to overemphasize surgical treatment, while another confines his attention to psychosomatic aspects.

There is an excellent discussion of aviation problems with regard to persons with allergic sensitivity.

Discussants were fairly well in accord as to the usefulness of radium in the treatment of hypertrophied lymphatic tissue in the nasopharynx. However, the reviewer believes that it is now pretty well agreed that radium therapy has been overdone; it is the opinion of many rhinologists that x-ray therapy is much less dangerous and more effective in this condition.

Despite these criticisms, the reviewer believes that this little book, which takes only about two hours to read, is very worthwhile for any rhinologist.

* * *

HUMAN GROWTH—The Story of How Life Begins and Goes On, Based on the Educational Film of the Same Title. By Lester F. Beck, Ph.D., Associate Professor of Psychology, University of Oregon, and Margie Robinson, M.A. Harcourt, Brace and Company, New York. 1949. $2.00.

This book is a welcome addition to the literature on sex education for 'teen-age children.

It will surely be well received by the junior high school group to whom it is especially addressed, and by the various adults who deal with them on this subject. One noteworthy feature of the book is the number, variety and attractiveness of its illustrations. Another excellence is the fullness of the background material on general somatic growth against which the account of specific sexual changes takes its proper place as one important expression of human development. Commendable also is its direct style, with its straightforward, unsentimental description of the processes and significance of various aspects of sexual function, including intercourse.

Only in connection with pregnancy does the author seem to relay a few concepts which fall short of the modern ideal. For instance, he says that a missed menstrual period "warns" the mother of pregnancy (one could prefer a word like "heralds"); he mentions some experience of nausea as a matter of course, even though he minimizes it; he fails to substitute "contractions" for labor "pains." These are such minor details that they would not be worth mentioning except for the fact that we are in an era where young people are ready to profit by every reassurance of the naturalness and happiness of pregnancy and birth.

Perhaps the greatest value of the book is that it is a companion piece to a film of like name, and that each chapter ends with a set of stimulating questions and answers. Both of these devices tend to guarantee that the author will succeed in his intention of "contributing to mental health by a simple honest telling of the story of human growth and by providing a sound basis for discussion with others." For without open discussion one is never quite sure what an adolescent has understood, no matter how clear the text he reads.

* * *

BULLETIN ON NARCOTICS, No. 1, October 1949. United Nations, Department of Social Affairs, Lake Success, New York.

This is the first of a regular series of bulletins on the traffic in narcotics to be issued quarterly by the United Nations, thus continuing similar work initiated by the defunct League of Nations. Subjects considered in this issue are international control of narcotic drugs, opium production throughout the world, an enquiry into the coca leaf situation in South America, determining the origin of opium, and administrative matters pertaining to the commission on narcotics. There are illustrations of narcotic plants, cultivated areas, native plantation workers, maps of countries showing legal and illegal production of opium, laboratory assistants analyzing crude products, etc. The discussion on the origin of opium is disappointing as it contains nothing of historical interest; such material is better presented in current textbooks on pharmacology. In fact the scientific matter in this bulletin is so elementary and limited that it has nothing to offer to scientists and physicians. The bulletin is of interest only to regulation-makers and administrative authorities concerned with legal technicalities of the traffic in narcotics.

* * *

CYSTOSCOPY AND UROGRAPHY. By James B. MacAlpine, D.Sc., F.R.C.S., lately Honorary Surgeon and Surgeon in Charge of the Genito-urinary Department, Salford Royal Hospital. Third Edition, Revised. The Williams and Wilkins Co., Baltimore. 1949. $13.50.

The third edition of MacAlpine's book on "Cystoscopy and Urography" is a text for students, budding urologists, and the surgeon who does an occasional cystoscopy. There is very little change in this edition over the previous books, the first edition being published in 1927, the second in 1936. Chapters on renal tuberculosis and punch operation for prostatic hypertrophy have been added to the third edition. The book goes into meticulous detail about the cystoscope, its construction, ocular system, care, limitations, and general uses. Most of the commonly occurring diseases observed in the practice of office urology are discussed. There are excellent sections on urinary calculi, renal anomalies and the

technique of urography. A chapter on diseases of the prostate is included together with a discussion of transurethral prostatic resections as practiced in England. This important and live subject is dealt with inadequately and gives misleading ideas of present-day procedures and results. The same group of cases with the same high operative mortality described in the 1936 edition are again reported in the 1946 book. An incomplete channelling type of operation is again advised and no mention is made of the important advances and improvements in this procedure during the last decade.

Continued and careful study of the book reveals a wealth of material. The section on bladder tumors is especially well done, although the suggested massive cystoscopic coagulation of the larger papillomas is quite laborious and cumbersome when compared to present-day rapid and more thorough transurethral resection methods.

The book is easy to read, concise, easy to handle, printed on good paper, and the illustrations are numerous and well done. Especially commendable are the colored cystoscopic drawings, illustrating the different bladder lesions. Any failure to make this new edition as up-to-date as it might be is partly compensated for by emphasis on fundamentals that have stood the test of time; while not taking the place of our recently published urologic texts, this book is definitely an addition to the cystoscopist's library.

* * *

MAY'S MANUAL OF THE DISEASES OF THE EYE—For Students and General Practitioners. 20th Edition. Charles A. Perere, M.D., Assistant Clinical Professor, College of Physicians and Surgeons, Columbia University, N. Y. 378 Illustrations—32 plates with 93 colored figures. The Williams and Wilkins Co., Baltimore, Maryland, 1949. $5.00.

Since its first edition this book has become one of the American medical classics. As stated in the first edition, the book is intended as a concise, practical and systematic manual of the diseases of the eye for the medical student and the general practitioner of medicine.

The twentieth edition has been completely revised and reset, and many portions of the text have been rewritten. Many of the black-and-white illustrations of the 19th edition which had outlived their distinctness have been omitted or have been replaced by new cuts. The chapter on the diseases of the conjunctiva has been revised and under therapy the newer antibiotics have been discussed. The chapter on the diseases of the optic nerve has been rewritten. One wonders if the long chapter on the complicated subject of disturbances of motility of the eye has a place in a book of this character.

Dr. Perera is to be congratulated on the fact that in the rather extensive revision he has not changed the original purpose or character of the book.

The printing and general format are a distinct improvement over the preceding edition.

The book should maintain its popularity and continue to serve as a reliable and practical introduction to the practice of ophthalmology.

* * *

A SYNOPSIS OF MEDICINE. By Sir Henry Letheby Tidy, K.B.E., M.A., M.D., Extra Physician to H.M. the King, Consulting Physician to St. Thomas' Hospital. Ninth Edition, Revised and Enlarged. The Williams and Wilkins Co., Baltimore, 1949. $7.50.

Nine editions of this well-known English synopsis of medicine may "rather strongly imply usefulness" as one reviewer has said, but it is difficult to determine under what circumstances. To encompass all of medical knowledge in 1,146 pages and do justice to each subject is perhaps asking too much of any author, and Sir Henry has made a brave attempt. The book, however, leaves much to be desired in the way of accuracy, completeness and clarity. Controversial subjects, especially in the realm of therapy, are briefly disposed of with positive statements as though the issue were closed. Criteria for prognosis are set up which seem to be at best based on clinical impressions of the author's, and are at times at variance with the literature. Questionable statements as to etiology, pathology and symptomatology may be readily found. The outline form necessitates too much brevity, and numerous cross references further decrease the usefulness, even for a quick review. And yet the author stops to define "watery eyes—the tear that never drops"! Numerous lists of symptoms are given without indication of which are important and significant.

Examples of the above:

Page 665—"Malignant hypertension has no existence apart from malignant nephrosclerosis."

Page 665—"Physical signs of benign hypertrophy—Cardiac hypertrophy always develops."

Page 665—Treatment of benign hypertension by diet: "No red meat," "strict salt-free diet not advisable," "colonic irrigation once a week"!

Page 795—Histology of kidneys in malignant hypertension: "See benign hypertrophy, but all changes more advanced and more extensive."

In view of the above the reviewer does not believe that Tidy's "Synopsis of Medicine" in any way replaces the many excellent textbooks now available. It is useful as a compendium and has a great deal of valuable information and therefore may have a place for the student who is preparing for examination. It is, however, not recommended as a textbook for medical students desiring more extensive coverage of the field of medicine.

* * *

A TWENTIETH CENTURY PHYSICIAN, Being the Reminiscences of Sir Arthur Hurst, D.M. The Williams and Wilkins Company, Baltimore, 1949. $3.50.

Sir Arthur Hurst was well known in this country and his brilliant work was fully appreciated. But few realized the many facets of his interesting character which are revealed in this little book of memoirs. Hurst is a natural raconteur and one's interest never flags as he reads through the author's vivid recollections of his childhood, medical school experiences, and thus on through his varied and exciting career. The war passages are of especial interest and the thumbnail sketches of innumerable interesting and important people constantly surprise one with unexpected bits of information. It is greatly to be regretted that Sir Arthur's sudden death prevented the narrative from being carried through his later years. A few typographical errors, mostly in spelling of proper names—such as Trosseau for Trousseau—are to be found on pp. 99, 106, 175 and 181; they will no doubt be corrected in a subsequent printing.

* * *

AN ATLAS OF HUMAN SEX ANATOMY. By Robert Latou Dickinson, M.D., F.A.C.S. A Topographical Hand Atlas. Medical Aspects of Human Fertility Series Issued by the National Committee on Maternal Health. Second Edition. 1949. $10.00.

Your reviewer cannot refrain from quoting the introductory paragraph of the preface to the second edition because it describes so poignantly the intent behind the compilation of facts and factors which make up the substance of Dickinson's "Atlas of Human Sex Anatomy." Dickinson expressed his reason for bringing forth a book on sex anatomy as follows:

"The first principle of sex education and marriage counselling gives attitudes precedence over anatomies. Yet function has structure for its machinery, and evasion of instruction concerning anatomy in action is in part responsible for the physical discord alleged by participants to be the

original cause for half the marital maladjustments and three-fourths of the divorces and desertions. We in medicine, therefore, are called upon to do our part to persuade morals to wed normals, to induce theology to adopt biology, to integrate within a workable code of ethics a sane science of sex."

This is a singular book in many respects. It encompasses an immense number of observations gathered during many years of a busy practice. It contains facts about female sex anatomy together with those of the male in the same volume, and it correlates them. It is exhaustive in its scope. It is well and abundantly illustrated by several artists and by the author who is no mean artist in his own right. It contains factual information free of sensual details and exaggerations and it presents the links in the chain of sex functions in an orderly way and without apology.

The first edition (1933) must have been in demand sufficiently to prompt the publishers to venture another and better edition. Your reviewer recalls that the first edition had difficulty in gaining recognition but evidently did after the value of the Atlas became recognized. In the second edition some new material concerned with the function of the male sex organ and spermatogenesis has been added. There are various references to Kinsey's book on sex behavior in the male and the author contrasts his observation with those of Kinsey. Here and there minor changes have been made in the text and in the illustrative material, but in general there are no great changes in the substance of the book.

Dickinson's Atlas, by its very nature, has a limited usefulness. Marriage and family counsellors, students of sex and infertility, psychologists and anybody interested in the problems of procreation and copulation will find this book of interest. It is not a book for prudes nor for the mentally immature and does not belong on the parlor table.

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GREEN'S MANUAL OF PATHOLOGY. Revised by H. W. C. Vines, M.A., M.D., Professor of Pathology, University of London, Dean, Charing Cross Hospital Medical School. 17th Edition. The Williams and Wilkins Company, Baltimore, 1949. $8.00.

This book is a clear presentation of the classical lesions of pathologic anatomy, and there are notes on the functional significance of many of these as well as discussions of pathogenesis in an effort to emphasize the dynamic nature of disease processes. Emphasis is placed upon systemic pathology, and much less than half of the book is devoted to general pathology. This leads to considerable fragmentation of the discussions of diseases like tuberculosis which affect many different organs.

Principal attention is given to well-defined diseases and the presentations are inclined to be dogmatic. Allusions are made to investigative work but no lists of references are given. The illustrations on the whole are well chosen and good. The text should be useful in teaching beginning students in pathology but it would not be a very satisfactory reference book.

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DISTRICT NURSING—A Handbook for District Nurses and for All Concerned in the Administration of a District Nursing Service. Eleanor Jeanette Merry, S.R.N., S.C.M., C.S.P., H.V. Cert. Education Officer, Queen's Institute of District Nursing, and Iris Dundas Irven, S.R.N., S.C.M., H.V. Cert. of R.S.I., Superintendent Worcester City Nursing Administration. The Williams and Wilkins Company, Baltimore, 1948. $4.00.

To practitioners in a country continuously disturbed by cries of the high cost of hospitalization, this comprehensive little manual will strike a note of deep interest. Many of the practices described in it are no longer customary in the larger cities of this land, but if ever we return to realistic financing of our state and national debt, it is not improbable that many of them will come back.

The manual is divided into 19 chapters, and ranges through a short history of district nursing, the organization of one of the London institutes of district nursing and suggestions for the training and conduct of district nurses. There are useful chapters on record keeping, simple nursing techniques, and home nursing of certain special diseases. There are illustrated sections on the performance of simple deliveries, simple tonsillectomy and so forth in the home, with suggestions for the district nurse's duties.

There are excellent chapters on the simpler elements of nutrition, family health teaching and the prevention of accidents in the home.

Finally there is a brief discussion of social insurance, vital statistics and the operation of the National Health Service Act.

Every general practitioner and most practitioners in smaller or rural areas are thoroughly familiar with the large amount of competent medical care which may be given in the patient's home, especially if a visiting nurse is available. Well organized district nurses' groups and general medical practitioners will find the manual of value. This reviewer would suggest that there should be a glossary of terms commonly used in Great Britain with suitable translation for readers in the U. S. A. Such terms as "Jeyes' fluid," "Benger's" and "Marmite" are household words in England, but would probably be unintelligible to the average Usanian. The book is neatly printed, of convenient size and readable.

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OBSTETRICS AND GYNECOLOGY—A Synoptic Guide to Treatment. By Beatrice M. Willmott Dobbie, M.A., M.B., F.R.C.S., D.M.R.E., Honorary Surgeon, Birmingham and Midland Hospital for Women. With 22 illustrations. Paul B. Hoeber, Inc., Medical Book Department of Harper and Brothers, New York, 1949. $5.50.

The book is of mediocre quality and contains nothing of any particular value.

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MODERN PRACTICE IN OPHTHALMOLOGY — 1949. Edited by H. B. Stallard, M.B.E., M.A., M.D., F.R.C.S., Surgeon, Moorfields, Westminster and Central Eye Hospital, London. Paul B. Hoeber, Inc., 1949. $12.50.

This book is one of a series of medical books published under the general editorship of Lord Horder under the group title of "Modern Practice Series." As pointed out in the preface, the purpose of the book is "to give the general practitioner an outline of the modern practice of ophthalmology. It is intended to be a guide to which he may refer when he shares with the eye specialist the responsibility of treating a case of ocular disease and when it falls to his lot to deal with a case in some remote part where there is inevitable delay in obtaining the advice of a consultant."

The book, written under the editorship of H. B. Stallard, assisted by 13 contributors, is midway in its scope between the small textbook usually used by medical students and the textbooks for the student or practitioner of ophthalmology.

The material is arranged in the accepted manner employed in textbooks and on the whole is well chosen, going into sufficient detail to be of value to the practitioner but without doing so to the extent that the subject becomes confusing. The book contains 231 black-and-white, well-chosen and well-printed illustrations. The 30 color plates are excellent as to the choice and the printing. The comprehensive index is particularly noteworthy.

While the selection of material, in general, is excellent, one wonders if the 56 pages devoted to refractions are justified in a book of this type. It would seem better to devote this space to more detailed accounts of treatment of ocular conditions, especially the emergency treatment of ocular

injuries. While the book was written by various contributors it would seem wise to have all the therapeutic recommendations either in the metric or apothecary system rather than a mixture of the two.

The quality of the paper, the printing and the binding are outstanding.

The book should be a very welcome addition to the library of the general practitioner who may at times have to care for eye cases.

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SURGERY OF THE HAND. By Sterling Bunnell, M.D. Second Edition. Philadelphia, London and Montreal. J. H. Lippincott Co., 1948.

This book had to be written some time, and it was magnificently achieved first in 1944, and again in 1948 by the same author, internationally recognized as the master surgeon in this field. The development of surgery of the hand to its present high degree has been due in large measure to his unique skill in the three divisions of surgery most concerned in reconstruction of the hand: Plastic surgery, neurosurgery and orthopedic surgery. His ability to treat the hand as an entity, to correct all the disabilities involved, led over the years to a remarkable development of fundamental principles, of ingenious methods and devices, of brilliantly conceived innovations which promise the present maximum possible reconstruction of the badly maimed hand.

From the first chapters on the phylogeny and comparative and normal anatomy of the hand, subjects to which the author brings unique and instructive information, to the making of new thumbs and the transplantation of tendons and nerves, the book is replete with suggestions and methods of great value to every surgeon who is engaged in caring for fresh injuries, burns and infections of the hand, or who is interested in restoring to as complete normality as possible the hand maimed or crippled by these various types of trauma.

Particularly important and instructive are the sections on skin grafting, on the preparation of pedicles, on the transplantation of bones, nerves, even whole fingers, on the restoration of prehension in the absence of a thumb, on the immediate care of infections of the hand and fingers and on the use of anatomically sound incisions which will not increase the residual disabilities that frequently spring from such infections and which can be reduced to a minimum by proper care at the moment of injury or at the time when drainage becomes necessary.

Also, the ingenious methods employed by Bunnell and his associates to correct congenital malformations of the hand are excellently portrayed. The presentation of tumors of the hand by Dr. L. D. Howard, Jr., adds a distinctive and important chapter to the surgical understanding of the hand.

The value of the book is greatly enhanced by numerous excellent illustrations that tell, better than words, the methods and devices employed in securing the best possible function as well as the best appearance of the restored hand.

Patients and surgeons alike will reap untold benefit from this truly monumental work, which makes available to present and succeeding generations the many experiences and the abundant technical knowledge acquired in the lifetime of a busy and talented surgical genius who for many years has made reconstruction, particularly of the crippled hand, his paramount interest.

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DIABETES AND ITS TREATMENT. By Joseph H. Barach, M.D., F.A.C.P., Associate Professor of Medicine, University of Pittsburgh. Oxford University Press, New York, 1949. $10.00.

"This book was not written for Charles Best, the co-discoverer of insulin, nor for the many other research scientists and clinicians who are outstanding authorities in this field. This book offers the general medical man a clinical approach to an understanding of the disease and its treatment." (Preface, p. viii.)

While the former statement is probably quite true, this reviewer does not believe that the latter statement has been well met. The first chapter deals with the history of diabetes and is good in that the many early workers in the field are adequately covered by a brief statement. However, as we get further into the book this fine attribute of a brief and adequate coverage is lost, and we must consider many paragraphs to pick out the basic ideas that have been expressed. Many aspects of the disease are covered in great detail, and as such are interesting to the specialist. But for the general practitioner and the student, the mass of detail accompanying each principle tends to negate the value of these principles and impress one that this is an almost hopelessly complex disease.

Included in the book are some 180 pages of diets and recipes whose value as stated is their easy reference by the patient. This seems unnecessary, for many of the diets vary little from each other in the number of calories but get their variety in altering the ratios of protein, fat, and carbohydrate, which for most patients complicates the picture even more.

The author's concept of the use of salt in heart disease and hypertension is fallacious in that he recommends use of intravenous salt solution for patients with heart disease of Grades I and II and Ringer solution for those with Grades III and IV and again in his recommendation of Eka as a salt substitute in hypertension (Eka is a combination of sodium citrate and sodium malleate).

On the whole, while the author maintains a scholarly and broadminded attitude on the controversial points in present day diabetic management, it is difficult to see where this book helps the average practitioner in the treatment of patients.